Ultrasound Obstet Gynecol 2015; **45**: 689–697
Published online 27 April 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14789

Uterine artery pulsatility index in the three trimesters of pregnancy: effects of maternal characteristics and medical history

A. TAYYAR*, L. GUERRA*, A. WRIGHT†, D. WRIGHT† and K. H. NICOLAIDES*

**Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK; †Institute of Health Research, University of Exeter, Exeter, UK*

KEYWORDS: first-trimester screening; pre-eclampsia; pyramid of pregnancy care; second-trimester screening; third-trimester screening; uterine artery Doppler

ABSTRACT

Objective *To define the contribution of maternal variables that influence the measured uterine artery pulsatility index (UtA-PI) in screening for pregnancy complications.*

Methods *Maternal characteristics and medical history were recorded, and UtA-PI was measured, in women with a singleton pregnancy attending for three routine hospital visits at 11 + 0 to 13 + 6 weeks, 19 + 0 to 24 + 6 weeks and 30 + 0 to 34 + 6 weeks or 35 + 0 to 37 + 6 weeks' gestation. For pregnancies delivering phenotypically normal live births or stillbirths at ≥ 24 weeks' gestation, variables from maternal demographic characteristics and medical history that are important in the prediction of UtA-PI were determined from linear mixed-effects multiple regression.*

Results *UtA-PI was measured in 90 484 cases in the first trimester, 66 862 cases in the second trimester and 33 470 cases in the third trimester of pregnancy. Significant independent contributions to UtA-PI were provided by gestational age, maternal age, weight, racial origin and a history of pre-eclampsia (PE) in the previous pregnancy. Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured UtA-PI and express the values as multiples of the median (MoM). The model was shown to provide an adequate fit of MoM values for all covariates both in pregnancies that developed PE and in those that did not.*

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

INTRODUCTION

Pre-eclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality, affecting 2–3% of all pregnancies[1–3]. Within the last decade, extensive research has been devoted to screening for PE with the aims of firstly, reducing the prevalence of the disease through pharmacological intervention in those at high risk[4,5] and secondly, minimizing adverse perinatal events for those who develop PE, by determining the appropriate time and place for delivery[6]. Our approach to risk assessment and screening for PE 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 made at different times during pregnancy[7–9]. However, in the application of Bayes' theorem in combined screening for PE, it is essential to standardize the measured values of biomarkers for any variables included in the prior model.

PE is thought to be a consequence of impaired placentation manifested in increased impedance to flow in the uterine arteries (UtAs)[10–12]. Several UtA Doppler studies have reported that, in pregnancies that develop PE, especially in those requiring early delivery, the pulsatility index (PI) is increased in the first, second and third trimesters of pregnancy[13–21]. However, UtA-PI depends on variables from maternal characteristics and medical history and, for its effective use in risk assessment and screening, these covariates need to be taken into account. This can be achieved by standardizing UtA-PI levels into multiples of the normal median (MoM) values.

The objectives of this study were first, to identify and quantify the effects that variables from maternal characteristics and medical history have on UtA-PI levels;

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London, SE5 9RS, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 9 January 2015

second, to present a model for standardizing UtA-PI measurements into MoM values; and third, to summarize the distribution of MoM values in pregnancies with normal outcomes and in those that subsequently develop PE. The main focus of this paper is on pregnancies with normal outcome. Further details of the distribution of MoM values in pregnancies with PE and the use of UtA-PI in risk assessment will be presented in a separate paper.

METHODS

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for three routine hospital visits at King's College Hospital, University College London Hospital, and Medway Maritime Hospital, UK, between January 2006 and March 2014. In the first visit, at 11 + 0 to 13 + 6 weeks' gestation, we recorded maternal characteristics and medical history, and combined screening for aneuploidies was performed[22]. The second visit, at 19 + 0 to 24 + 6 weeks' gestation, and third visit, initially at 30 + 0 to 34 + 6 weeks and subsequently at 35 + 0 to 37 + 6 weeks, included an ultrasound examination of the fetal anatomy and an estimation of fetal size from measurements of fetal head circumference, abdominal circumference and femur length. Gestational age was determined by measurement of fetal crown–rump length (CRL) at 11–13 weeks or the fetal head circumference at 19–24 weeks[23,24].

Written informed consent was obtained from the women agreeing to participate in this study on adverse pregnancy outcome, which was approved by the ethics committee of each participating hospital. Inclusion criteria were a singleton pregnancy delivering a phenotypically normal live birth or stillbirth at or after 24 weeks' gestation. We excluded pregnancies with aneuploidies or major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks.

Patient characteristics

Patient characteristics included 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), cigarette smoking during pregnancy (yes/no), history of chronic hypertension (yes/no), history of pre-existing diabetes mellitus Type 1 or 2 (yes/no), history of systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), family history of PE in the mother of the patient (yes/no) and obstetric history including parity (parous/nulliparous if no previous pregnancies at or after 24 weeks), previous pregnancy with PE (yes/no), gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal height was measured at the first visit and weight at each visit.

Uterine artery pulsatility index

First- and third-trimester Doppler studies were carried out transabdominally, but in the second trimester the transvaginal route was used because cervical length was also measured. At 11 + 0 to 13 + 6 weeks' gestation, a sagittal section of the uterus was obtained and the cervical canal and internal cervical os were identified. Subsequently, the transducer was tilted gently from side to side and color-flow mapping was used to identify each UtA along the side of the cervix and the uterus, at the level of the internal os[13,14]. At 19 + 0 to 24 + 6 weeks, women were asked to empty their bladder and were placed in the dorsal lithotomy position. The ultrasound probe was inserted into the vagina and advanced in turn into the left and right lateral fornices. The UtAs were identified using color Doppler, at the level of the internal cervical os[25]. At 30 + 0 to 37 + 6 weeks, color Doppler was used to identify each UtA at the apparent crossover with the external iliac arteries[15].

After identification of each UtA, pulsed-wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel. Care was taken to ensure that the angle of insonation was less than 30° and the peak systolic velocity was greater than 60 cm/s to ensure that the UtA, rather than the arcuate artery, was being examined. When three similar waveforms had been obtained consecutively, the PI was measured and the mean PI of the left and right arteries was calculated.

All Doppler studies were carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (www.fetalmedicine.com).

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric gestational hypertension (GH).

The definitions of GH and PE were those of the International Society for the Study of Hypertension in Pregnancy[26]. GH was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, on at least two occasions 4 h apart, developing after 20 weeks' gestation in previously normotensive women. PE was defined as GH with proteinuria ≥ 300 mg within 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection was available. PE superimposed on chronic hypertension was defined as significant proteinuria (as defined above) developing after 20 weeks' gestation in women with known chronic hypertension

Table 1 Maternal and pregnancy characteristics of women with singleton pregnancy attending for routine visits between January 2006 and March 2014, according to trimester of pregnancy

Characteristic	*11 + 0 to 13 + 6 weeks (n = 90 484)*	*19 + 0 to 24 + 6 weeks (n = 66 862)*	*30 + 0 to 37 + 6 weeks (n = 33 470)*
Maternal age (years)	31.3 (26.8–35.1)	30.8 (26.2–34.7)	31.3 (26.8–35.0)
Maternal weight (kg)	66.0 (59.0–76.0)	70.0 (63.0–80.5)	75.9 (68.0–86.0)
Maternal height (cm)	164.0 (160.0–169.0)	164.0 (160.0–168.7)	164.6 (160.0–169.0)
GA at examination (weeks)	12.7 (12.3–13.1)	22.2 (21.6–22.7)	32.4 (32.0–33.2)
Racial origin			
Caucasian	66 052 (73.0)	46 589 (69.7)	23 433 (70.0)
Afro-Caribbean	15 085 (16.7)	13 746 (20.6)	6300 (18.8)
South Asian	4727 (5.2)	3232 (4.8)	1895 (5.7)
East Asian	2375 (2.6)	1636 (2.4)	1020 (3.0)
Mixed	2245 (2.5)	1659 (2.5)	822 (2.5)
Medical history			
Chronic hypertension	1158 (1.3)	966 (1.4)	451 (1.3)
Diabetes mellitus	743 (0.8)	574 (0.9)	314 (0.9)
SLE or APS	168 (0.2)	128 (0.2)	62 (0.2)
Cigarette smoker	8591 (9.5)	6630 (9.9)	3056 (9.1)
Family history of PE	3597 (4.0)	2510 (3.8)	966 (2.9)
Obstetric history			
Nulliparous	44 521 (49.2)	34 241 (51.2)	16 659 (49.8)
Parous with no previous PE	43 042 (47.6)	30 370 (45.4)	15 819 (47.3)
Parous with previous PE	2921 (3.2)	2251 (3.4)	992 (3.0)
Interpregnancy interval (years)	2.9 (1.9–4.9)	3.0 (1.9–5.0)	3.0 (2.0–4.9)
GA at delivery of previous pregnancy (weeks)	40.0 (39.0–40.0)	40.0 (39.0–40.0)	40.0 (39.0–40.0)
Birth weight of previous pregnancy (g)	3348 (3008–3689)	3348 (3000–3689)	3350 (3008–3690)
Mode of conception			
Spontaneous	87 019 (96.2)	64 640 (96.7)	32 232 (96.3)
Ovulation induction	1307 (1.4)	708 (1.1)	354 (1.1)
In-vitro fertilization	2158 (2.4)	1514 (2.3)	884 (2.6)
Pregnancy outcome			
PE	2160 (2.4)	1837 (2.7)	726 (2.2)
No PE	88 324 (97.6)	65 025 (97.3)	32 744 (97.8)

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

(history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease). The birth-weight *Z*-score for the neonate in the last pregnancy was derived from our reference range of birth weight for gestational age at delivery[27].

Statistical analysis

The effect on UtA-PI of the following variables from maternal characteristics and medical history were examined: maternal age, weight, height and racial origin, history of chronic hypertension, diabetes mellitus Type 1 or 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 time of assessment.

As part of an exploratory analysis, multiple linear regression models were fitted to $\log_{10}$UtA-PI within each trimester. Continuous variables were initially coded 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 error SD and a criterion of 0.1 SD was used to identify terms that had little substantive impact on model predictions. Residual analysis was used to assess the adequacy of the model.

Graphical displays of the relationship between gestational age and UtA-PI levels and the effects of maternal age, weight, height and other characteristics on UtA-PI MoM values were produced for the final model and for the final model with factor levels for continuous covariates. Having identified potential models for each trimester, a parsimonious model was selected to cover the data for the three trimesters combined. This model was fitted using a linear mixed model with random effects to represent between-women random effects. 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 statistical software package R (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis[28].

RESULTS

Characteristics of the study population

The maternal characteristics and medical history of the pregnant women that fulfilled the entry criteria are presented in Table 1. UtA-PI was measured in 90 484 cases in the first trimester, 66 862 cases in the second trimester and 33 470 cases in the third trimester. In the first phase of the study UtA-PI was measured only at the first-trimester visit, but this was subsequently extended to the second- and then the third-trimester visits. 20 140 UtA-PI measurements were recorded in all three trimesters, 36 196 measurements in the first and second trimesters, 4838 in the first and third trimesters, 3852 in the second and third trimesters, 29 310 in the first trimester only, 6674 in the second trimester only and 4640 in the third trimester only.

Variables affecting UtA-PI

Substantive contributions to UtA-PI levels were provided by gestational age, maternal age, weight, Afro-Caribbean racial origin, PE and birth-weight *Z*-score in the last pregnancy, but not by maternal height, family history of PE, diabetes mellitus, SLE or APS, smoking, method of conception or interpregnancy interval.

The effects of gestational age on median levels of UtA-PI were different for the three trimesters (Figure 1). A smooth relationship across the three trimesters would have been more satisfactory from a theoretical perspective. However, the empirical data provided little support for such a relationship and, consequently, trimester-specific effects were fitted for the final model.

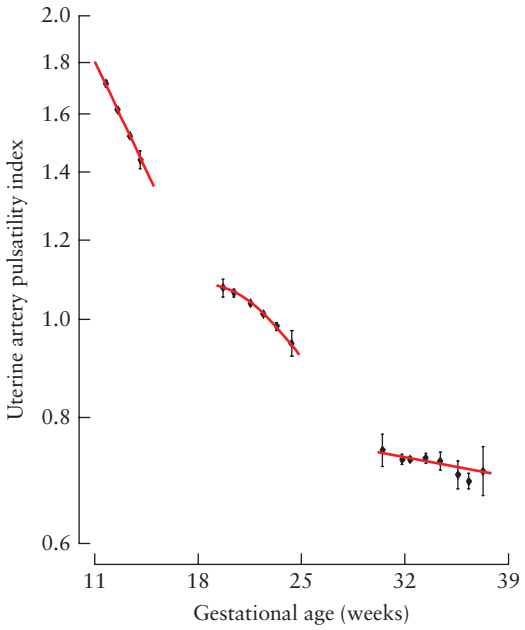

Figure 1 Relationship between median (95% CI) levels of uterine artery pulsatility index and gestational age across the three trimesters of pregnancy in women with singleton pregnancy attending for routine hospital visits.

The relationships between maternal age and weight and UtA-PI were dependent on gestational age (Figure 2). In the first trimester, there were negative trends with UtA-PI for both maternal age and weight, in the second trimester there were no substantive trends and in the third trimester UtA-PI increased as maternal age and weight increased. Therefore, interactions between maternal age and gestational age, and maternal weight and gestational

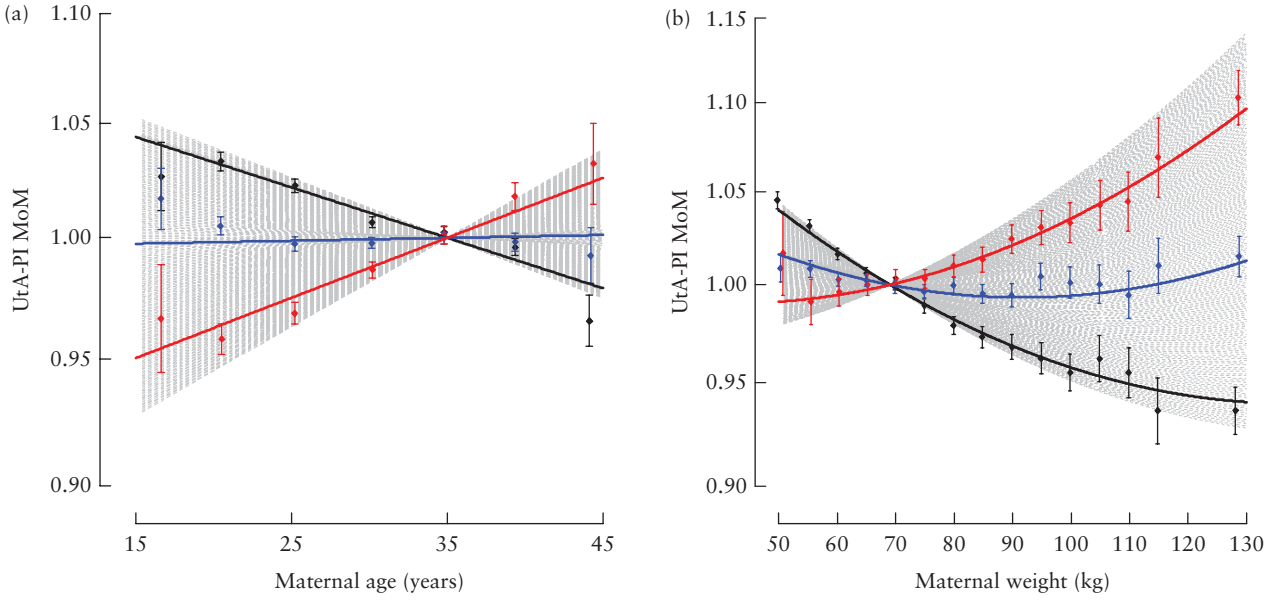

Figure 2 Effects of maternal age (a) and weight (b) on uterine artery pulsatility index (UtA-PI) (with 95% CIs) at 11 + 0 to 13 + 6 weeks' gestation (black), 19 + 0 to 24 + 6 weeks (blue) and 30 + 0 to 37 + 6 weeks (red), shown on multiples of the median (MoM) scale after correcting for other factors. Shaded areas show range of possible relationships between maternal age and weight with UtA-PI MoM for gestational age between 11 and 37 weeks.

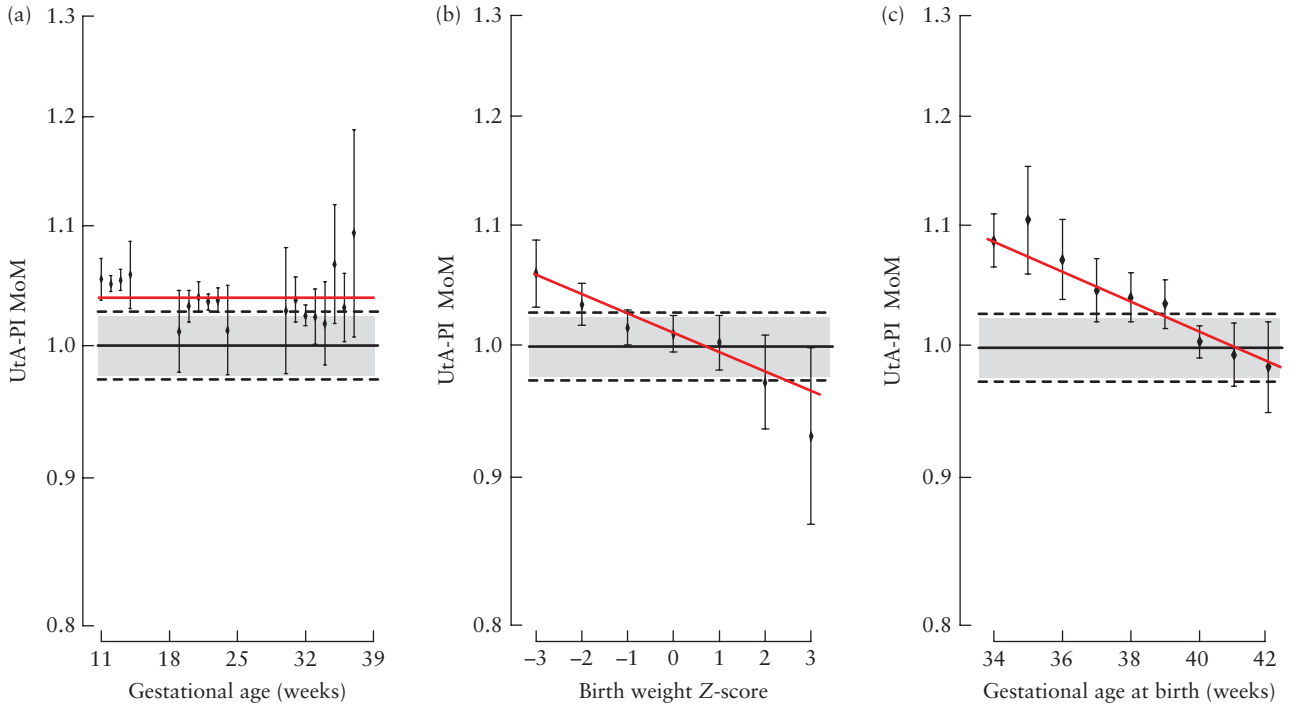

Figure 3 Effects of Afro-Caribbean racial origin (a), and birth-weight Z-score (b) and gestational age at birth (c) in last pregnancy in women with previous pre-eclampsia on median (95% CI) uterine artery pulsatility index (UtA-PI), plotted on multiples of the median (MoM) scale after correcting for other factors. Fitted effect (——), median MoM of 1.0 (——) and median MoM ± 0.1 SD (- - - -) are shown.

Table 2 Final model for calculating multiples of the median values for uterine artery pulsatility index

Term	*Estimate*	*95% CI*	*SE*	P
Intercept	0.255731426	0.25262117 to 0.258841680	0.001586864	< 0.0001
Trimester-dependent effects				
First trimester				
Gestational age (−77)*	−0.004407905	−0.004589789 to −0.004226022	0.000092798	< 0.0001
Second trimester				
Constant	−0.291978212	−0.372586668 to −0.211369756	0.041126763	< 0.0001
Gestational age (−77)*	0.002981682	0.000853557 to 0.005109808	0.001085778	0.003
(Gestational age (−77))^2*	−0.000030792	−0.000044787 to −0.000016797	0.000007140	< 0.0001
Third trimester				
Constant	−0.335511985	−0.356070864 to −0.314953105	0.010489224	< 0.0001
Gestational age (−77)*	−0.000396726	−0.000530898 to −0.000262554	0.000068455	< 0.0001
Trimester-independent effects				
Weight				
Weight (−69)†	−0.000888890	−0.000952565 to −0.000825215	0.000032487	< 0.0001
(Weight (−69))^2†	0.000006006	0.000004291 to 0.000007722	0.000000875	< 0.0001
(Weight (−69))†× (gestational age (−77))*	0.000008322	0.000007699 to 0.000008944	0.000000317	< 0.0001
Age				
Age (−35)‡	−0.001117349	−0.001257511 to −0.000977187	0.000071511	< 0.0001
(Age (−35))‡× (gestational age (−77))*	0.000015061	0.000013551 to 0.000016570	0.000000770	< 0.0001
Racial origin				
Afro-Caribbean	0.018069553	0.016314558 to 0.019824549	0.000895406	< 0.0001
Obstetric history				
Parous with previous PE	0.004971474	0.000439828 to 0.009503120	0.002312064	0.0158
Parous with previous PE: birth-weight Z-score of last pregnancy	−0.006836336	−0.009737177 to −0.003935496	0.001480021	< 0.0001
Parous with previous PE: gestational age at delivery of last pregnancy (−40)§	−0.005119599	−0.006828085 to −0.003411114	0.000871676	< 0.0001

Continuous variables were centered by subtracting the mean from each measured value: *77 from gestational age in days; †69 from maternal weight in kg; ‡35 from maternal age in years; §40 from gestational age at delivery in weeks. PE, pre-eclampsia; SE, standard error.

age were included in the model, such that the relationship between UtA-PI and maternal age or weight was, in part, defined by gestational age. The shaded regions in Figure 2 show the range of possible relationships between maternal age or weight and UtA-PI MoM for any given gestational age between 77 and 259 days (11–37 weeks' gestation). These effects are relatively small and, over the effective range of maternal age and weight, they account for less than 0.5 SDs on the log-MoM scale.

In women of Afro-Caribbean racial origin, UtA-PI did not change substantially with gestational age (Figure 3). In parous women who developed PE in their previous pregnancy, UtA-PI was inversely related to the birth-weight *Z*-score and gestational age at birth of their last pregnancy, and the effect was similar across all three trimesters (Figure 3).

Final model for calculation of UtA-PI MoM

A linear mixed model with random effects to represent between-women random effects was fitted to the subset of variables that contributed substantively to the linear regression models (Table 2). Trimester effects were included, the first trimester being used as the reference. For relationships assumed to be constant, such as Afro-Caribbean racial origin, common effects were fitted. For relationships assumed not to be constant across the three trimesters, such as gestational age, trimester-specific effects were fitted.

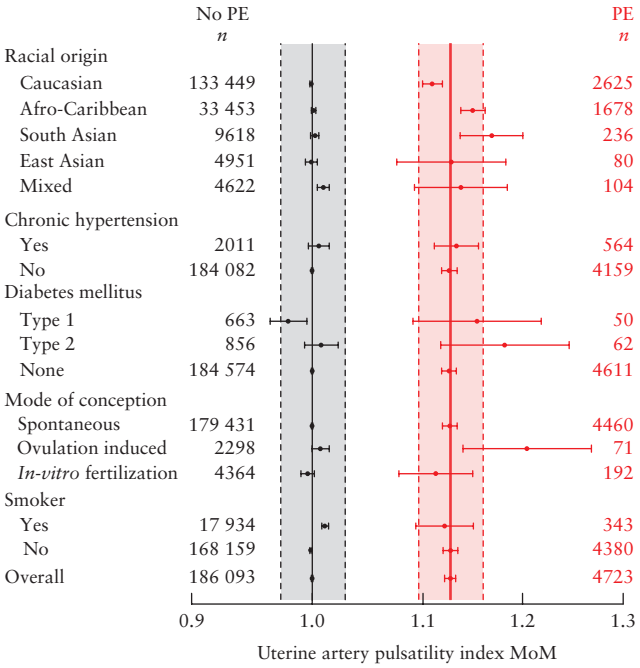

Figure 4 Median uterine artery pulsatility index multiples of the median (MoM) (with 95% CIs) derived from the model, according to racial origin, chronic hypertension, diabetes mellitus, method of conception and smoking in pregnancies that were unaffected by pre-eclampsia (PE) (black values) and those that developed PE (red values). Median MoM of 1.0 (——) and median MoM ± 0.1 SD (- - - -) of women unaffected by PE and median MoM of 1.137 in women with PE (——) and median MoM ± 0.1 SD of women unaffected by PE (- - - -) are indicated.

MoM diagnostics for categorical variables in pregnancies unaffected by PE and those that developed PE are shown in Figure 4. Diagnostics for the effect of gestational age in nulliparous women and parous women with and without a history of PE, with current pregnancies unaffected by PE and for those that developed PE, are shown in Figure 5. In unaffected pregnancies, the model provided an adequate fit, with median MoM values falling well within 0.1 SD of 1 MoM. In the PE group, the overall median MoM was 1.137 (95% CI, 1.132–1.143) and there was a consistent increase over normal levels across the range of variables.

Distributional properties of UtA-PI MoM values

Figure 6 shows a Gaussian distribution of UtA-PI MoM values. The median and 5th, 10th, 90th and 95th percentiles were 1.0000 (95% CI, 0.99854–1.00167), 0.63851 (95% CI, 0.63664–0.6401), 0.70748 (95% CI, 0.70594–0.70894), 1.4162 (95% CI, 1.41341–1.41924) and 1.56599 (95% CI, 1.56167–1.57024), respectively. Estimated SDs and correlations, with 95% CIs, are given in Tables 3 and 4, respectively. The SDs were very similar but decreased slightly with a later trimester. The correlations between $\log_{10}$UtA-PI MoM across trimesters were slightly stronger for first and second, and second and third, trimesters than for first and third trimesters.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that, in pregnancy, significant independent contributions to the measured UtA-PI are provided by maternal characteristics and variables from medical history. UtA-PI decreases with increased gestational age, decreases with increased maternal age and weight in the first trimester and increases in the third trimester, and is higher in women of Afro-Caribbean racial origin. In parous women who developed PE in a previous pregnancy, UtA-PI is inversely related to the gestational age at birth, being high in those with an early-preterm birth, and birth-weight *Z*-score, being high for very small neonates and low for macrosomic neonates.

Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured UtA-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 developed PE and in those without this complication.

Strengths and limitations of the study

The strengths of this study are first, the prospective examination of a large population of pregnant women attending for routine care in three well-defined gestational-age

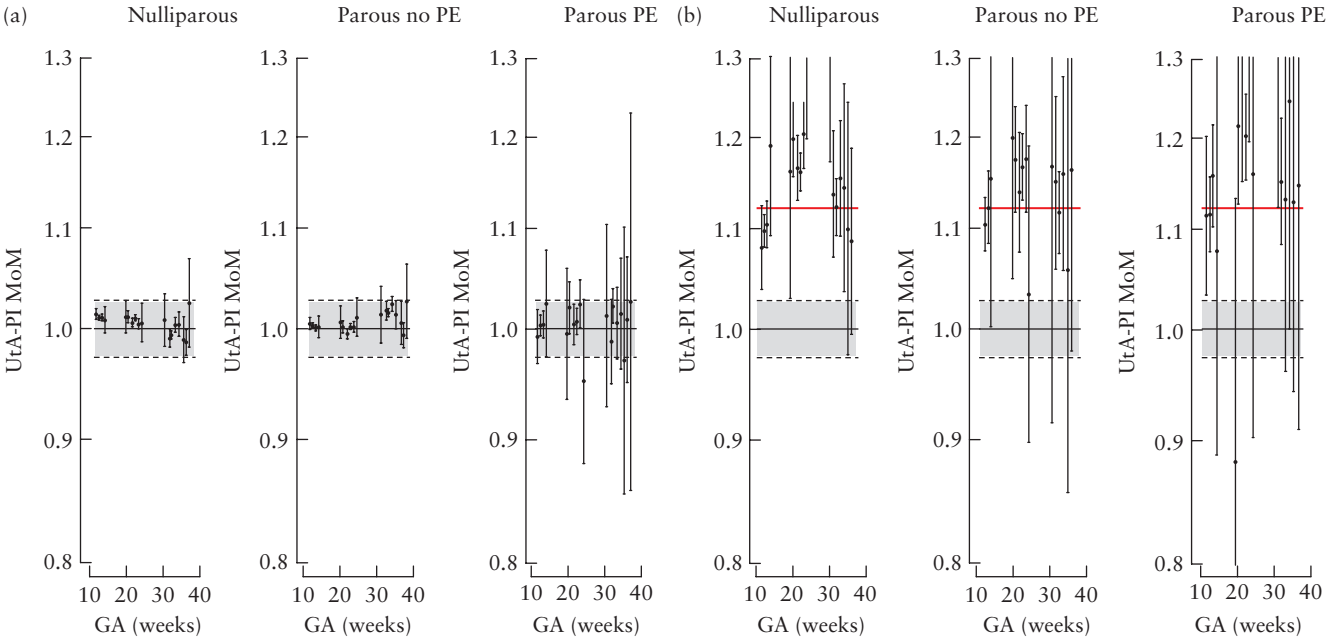

Figure 5 Median (95% CI) uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) according to gestational age (GA), derived from the model in nulliparous women and in parous women with and without prior history of pre-eclampsia (PE) in pregnancies unaffected by PE (a) and those that developed PE (b). Median MoM of 1.0 (——) and median MoM ± 0.1 SD (- - - -) of women unaffected by PE and median MoM of 1.137 in women with PE (——) are indicated.

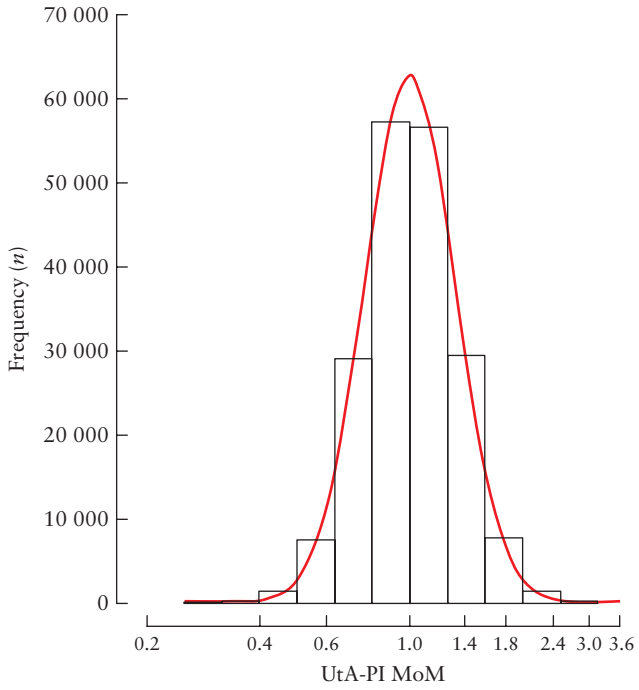

Figure 6 Gaussian distribution of uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) values.

Table 3 SDs for $\log_{10}$uterine artery pulsatility index multiples of the median values according to trimester of pregnancy

Trimester	*SD Estimate (95% CI)*
First	0.12813 (0.12763–0.12865)
Second	0.11525 (0.11479–0.11571)
Third	0.11377 (0.11332–0.11423)

Table 4 Correlation of $\log_{10}$uterine artery pulsatility index multiples of the median (MoM) values between the three trimesters of pregnancy

Trimester	*Second trimester*	*Third trimester*
First	0.46776 (0.45677–0.47862)	0.29861 (0.28582–0.31129)
Second	1	0.3985 (0.38667–0.41020)
Third	—	1

Values in parentheses are 95% CI.

ranges that are widely used for the first-trimester screening of chromosomal defects and second- and third-trimester assessment of fetal anatomy, growth and wellbeing; second, use of a standardized methodology for measurement of UtA-PI by appropriately-trained doctors; and third, application of multiple regression analysis to define the contribution and interrelationships of maternal variables that influence the measured UtA-PI across the three trimesters of pregnancy.

An alternative to the use of data from three gestational-age ranges would have been to perform a cross-sectional study with inclusion of each gestational week, from the beginning to the end of pregnancy. Such an approach could have overcome the discontinuity observed in the relationship between UtA-PI and gestational age, which necessitated the fitting of trimester-specific effects in the model. A plausible explanation for the observed

discontinuity is the effect of errors in the estimation of gestational age and range restriction close to the lower and upper ends of the allowed measurement ranges. For example, in the first trimester, gestational age is derived from fetal CRL, and the lower and upper allowed measurements of 45 mm and 84 mm correspond to 11 + 0 and 13 + 6 weeks' gestation. In reality, any given true gestational age is likely to have a distribution of CRL measurements that are truncated at the prespecified cut-offs of 45 mm and 84 mm. The combination of errors in variables and range restriction will distort the underlying relationship[29].

Comparison with findings of previous studies

In screening by biochemical markers, the principle that the measured concentrations should be expressed as MoMs, after adjustment for maternal characteristics that affect the measurements in unaffected pregnancies, is well established[30,31]. We have advocated that the same rationale should apply to the use of biophysical markers in screening for pregnancy complications[8,18,20,32]. In previous smaller studies examining the potential value of UtA-PI in screening for PE in the first, second or third trimesters, we used multiple regression analysis to express the measurements as MoMs[8,9,18–20]. In this expanded series of pregnancies in all three trimesters, we developed a model that incorporates variables with common effects across the trimesters and those with trimester-specific effects.

Implications for clinical practice

Effective use of UtA-PI in risk assessment and screening necessitates that variables from maternal characteristics and medical history that affect this measurement in normal pregnancies should be taken into account. To illustrate the need for standardizing into MoM values, consider a pregnancy at 12 weeks' gestation in a 35-year-old nulliparous Caucasian woman with a weight of 69 kg. If the UtA-PI is 1.9, the measurement is translated into a MoM value of 1.14, which is on the 67th percentile for normal pregnancies and similar to the overall median MoM in pregnancies with PE. For a parous woman with the same characteristics but a history of PE delivering at 34 weeks' gestation a neonate with a birth-weight *Z*-score of −3 SD, the same UtA-PI corresponds to a MoM value of 1.00, which is on the 50th percentile for normal pregnancies. Consequently, for the same UtA-PI, the risk for PE would depend on the history of PE.

In screening for PE by UtA-PI in isolation, UtA-PI would act as a proxy for other risk factors, including maternal weight and history of PE, and in such cases correction for these factors might well be counterproductive. However, our approach to risk assessment and screening is to use Bayes' theorem to combine information on maternal characteristics with that obtained from biomarkers. This involves a prior model incorporating the effect of maternal characteristics[7]. In this approach, the contribution of biomarkers such as UtA-PI is the additional information they provide over that already captured in the prior model. To achieve this, the distribution of UtA-PI should be specified conditionally on the variables included in the prior distribution, such as maternal weight and history of PE, otherwise the contribution of these variables to risk assessment is overestimated.

ACKNOWLEDGMENTS

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116) and by the European Union 7th Framework Programme -FP7-HEALTH-2013-INNOVATION-2 (ASPRE Project # 601852).

REFERENCES

1. World Health Organization. *World Health Report: 2005 – Make every mother and child count*. Geneva, Switzerland: World Health Organization, 2005.
2. *Confidential Enquiry into Maternal and Child Health (CEMACH) Perinatal Mortality 2006: England, Wales and Northern Ireland*. CEMACH: London, UK, 2008.
3. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; **33**: 130–137.
4. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguère Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402–414.
5. Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, Ebrashy A, Bujold E. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141–146.
6. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KW, Drogtrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, van Loon AJ, Lub A, Papatsonis DN, van der Post JA, Roumen FJ, Scheepers HC, Willekes C, Mol BW, van Pampus MG; HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; **374**: 979–988.
7. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015 (in press).
8. Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012; **32**: 171–178.
9. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013; **33**: 8–15.
10. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. *J Pathol Bacteriol* 1967; **93**: 569–579.
11. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for gestational age infants. *Br J Obstet Gynaecol* 1986; **93**: 1049–1059.
12. Pijnenborg R. The placental bed. *Hypertens Pregnancy* 1996; **15**: 7–23.
13. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11–14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 583–586.
14. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2008; **32**: 138–146.
15. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
16. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol* 2001; **18**: 441–449.
17. Yu CK, Smith GC, Papageorghiou AT, Cacho AM, Nicolaides KH. An integrated model for the prediction of preeclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women. *Am J Obstet Gynecol* 2005; **193**: 429–436.

18. Gallo DM, Poon LC, Akolekar R, Syngelaki A, Nicolaides KH. Prediction of preeclampsia by uterine artery Doppler at 20–24 weeks' gestation. *Fetal Diagn Ther* 2013; **34**: 241–247.
19. Lai J, Poon LC, Pinas A, Bakalis S, Nicolaides KH. Uterine artery Doppler at 30–33 weeks' gestation in the prediction of preeclampsia. *Fetal Diagn Ther* 2013; **33**: 156–163.
20. Tayyar A, Garcia-Tizon Larroca S, Poon LC, Wright D, Nicolaides KH. Competing risk model in screening for preeclampsia by mean arterial pressure and uterine artery pulsatility index at 30–33 weeks' gestation. *Fetal Diagn Ther* 2014; **36**: 18–27.
21. Pedrosa AC, Matias A. Screening for pre-eclampsia: a systematic review of tests combining uterine artery Doppler with other markers. *J Perinat Med* 2011; **39**: 619–635.
22. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. *Prenat Diagn* 2011; **31**: 7–15.
23. Robinson HP, Fleming JE. A critical evaluation of sonar "crown–rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
24. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
25. Papageorghiou AT, To MS, Yu CK, Nicolaides KH. Repeatability of measurement of uterine artery pulsatility index using transvaginal color Doppler. *Ultrasound Obstet Gynecol* 2001; **18**: 456–459.
26. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; **20**: IX–XIV.
27. Poon LCY, Volpe N, Muto B, Syngelaki A, Nicolaides KH. Birthweight with gestation and maternal characteristics in live births and stillbirths. *Fetal Diagn Ther* 2012; **32**: 156–165.
28. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011; ISBN 3-900051-07-0, URL http://www.R-project.org/.
29. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010; **340**: c2289.
30. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. *Ultrasound Obstet Gynecol* 2008; **31**: 493–502.
31. Wright D, Spencer K, Kagan K, Tørring N, Petersen OB, Christou A, Kallikas J, Nicolaides KH. First-trimester combined screening for trisomy 21 at 7–14 weeks' gestation. *Ultrasound Obstet Gynecol* 2010; **36**: 404–411.
32. Wright A, Wright D, Ispas CA, Poon LC, Nicolaides KH. Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2015; **45**: 698–706.

