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Maternal cardiovascular function at 35–37 weeks' gestation: relation to maternal characteristics

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KEYWORDS: cardiac output; maternal cardiovascular function; maternal characteristics; third-trimester screening; total peripheral resistance

ABSTRACT

Objective *To examine the possible effects of maternal characteristics and obstetric and medical history on maternal cardiovascular parameters at 35–37 weeks' gestation.*

Methods *In 3013 singleton pregnancies at 35–37 weeks, maternal characteristics and medical history were recorded; uterine artery pulsatility index, mean arterial pressure (MAP) and maternal cardiovascular parameters were measured. Multivariable regression analysis was used to determine significant predictors of the cardiovascular parameters among gestational age (GA), maternal characteristics and medical history.*

Results *Multivariable regression analysis demonstrated that significant independent prediction of log_{10}cardiac output and log_{10}cardiac power was provided by GA, maternal age, weight, weight gain from the first trimester, height, racial origin, smoking, assisted conception and previous neonatal birth-weight Z-score in parous women. For log_{10}total peripheral resistance, significant prediction was provided by GA, maternal age, height, racial origin, chronic hypertension, diabetes mellitus, assisted conception, previous neonatal birth-weight Z-score and prior pre-eclampsia (PE) in parous women. For log_{10}stroke volume, significant prediction was provided by maternal age, height, racial origin, smoking, chronic hypertension and diabetes mellitus. For heart rate, significant prediction was provided by GA, weight, weight gain, height, racial origin, chronic hypertension, previous neonatal birth-weight Z-score and prior PE in parous women. For log_{10}MAP, significant prediction was provided by maternal weight, racial origin, family history of PE, chronic hypertension and diabetes mellitus. For log_{10}thoracic fluid capacity, significant prediction was provided by GA, maternal age, weight, height, racial origin and systemic lupus erythematosus or antiphospholipid syndrome. For log_{10}ventricular ejection time, significant prediction was provided by GA, weight, height and racial origin.*

Conclusion *Maternal cardiovascular parameters are affected by maternal characteristics and medical and obstetric history, and they should therefore be converted into multiples of the normal median adjusted for significant independent predictors before their inclusion in combined screening for PE.*

INTRODUCTION

Preterm pre-eclampsia (PE) is thought to be a consequence of impaired placentation, reflected in increased uterine artery pulsatility index (UtA-PI) and this biomarker, either on its own or in combination with mean arterial pressure (MAP) and serum placental growth factor, is useful in the prediction of preterm PE[1–6]. In contrast, UtA-PI measured in the first, second or third trimester shows little or no discriminatory power for the prediction of term PE[3,7]. There is some evidence that preterm PE and term PE are characterized by different hemodynamic profiles and that an important pathophysiological mechanism for term PE is maternal cardiac dysfunction. Preterm PE, which is often associated with the birth of small-for-gestational-age (SGA) neonates, is preceded by low cardiac output and high peripheral resistance and UtA-PI, whereas term PE, which is usually unaccompanied by SGA, is preceded by high cardiac output, low peripheral resistance and normal UtA-PI[8,9].

This study constitutes the first step in the assessment of maternal cardiovascular function as a method of screening for late PE. Our approach to risk assessment and screening for PE is to apply logistic regression to combine the

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a-priori risk from maternal characteristics and obstetric and medical history (maternal factors) with the measurements of biomarkers; however, in the application of logistic regression to combined screening for PE, it is essential to standardize the measured values of biomarkers for any variables included in the prior model by converting the measurements into multiples of the normal median (MoM) values.

METHODS

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit in the third trimester of pregnancy at King's College Hospital, London, UK and Medway Maritime Hospital, Kent, UK, between March 2015 and December 2015. This visit, which is held at 35 + 0 to 37 + 6 weeks' gestation, includes recording of maternal factors, ultrasonographic estimation of fetal weight and measurement of UtA-PI, MAP and maternal cardiovascular parameters. Gestational age (GA) was determined by measurement of the fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[10,11]. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the ethics committee of each participating hospital. The patients included in the study all had a pregnancy resulting in the live birth of a phenotypically normal baby.

Maternal factors

Maternal factors recorded included age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic lupus erythematosus or antiphospholipid syndrome and obstetric history including parity (parous or nulliparous if no previous pregnancy $\geq$ 24 weeks' gestation), previous pregnancy with PE (yes or no), neonatal birth-weight *Z*-score, corrected for GA at delivery[12], from previous pregnancy and time interval between the last delivery and conception of the current pregnancy in years. Maternal weight and height were measured, and weight gain between the weight recorded at the time of the 11–13-week scan and that at 35–37 weeks was calculated.

Maternal cardiovascular function

Cardiovascular function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK)[13]. Four dual-surface electrodes were applied across the maternal thorax and after 15 min of rest in a sitting position recordings were made for 5 min. The signal processing unit of the system determines the relative phase shift of electrical current between the input signal and the output signal; the phase shift occurs owing to instantaneous changes in blood flow in the aorta. Cardiac output is subsequently estimated as the product of stroke volume and heart rate, and total peripheral resistance is calculated as the product of cardiac output and MAP. This operator-independent technology has been validated in both non-pregnant and pregnant populations[14,15].

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy[16]. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to confirm that the condition was chronic hypertension, PE or GH. The newborn was considered to be SGA if its birth weight was less than the 10th percentile after correction for GA at delivery[12].

Statistical analysis

Descriptive data are presented as median and interquartile range for continuous variables and as *n* (%) for categorical variables. Normality was first assessed by the Shapiro–Wilk test then graphically with histograms and Q–Q plots. First, the observed measurements of the maternal cardiovascular parameters were $\log_{10}$transformed if their distributions were not Gaussian. Second, regression analysis was used to determine if GA at screening was a significant predictor of the maternal cardiovascular parameters. Third, the observed maternal cardiovascular parameters were expressed as MoMs, corrected for GA at screening if it provided a significant contribution. Fourth, multiple regression analysis was used to determine which of the maternal factors were significant predictors of GA-corrected cardiac output, total peripheral resistance, stroke volume, cardiac power, thoracic fluid capacity and ventricular ejection time; and heart rate and MAP, adjusted for hypertensive disorders of pregnancy and neonatal birth-weight *Z*-score in the index pregnancy. Fifth, the effects of maternal factors on cardiovascular parameters, corrected for GA at screening where applicable, are illustrated in plots of effect estimates. Sixth, in order to establish the MoM equations, backward multiple regression analysis was used to determine which of the maternal factors and GA at screening were significant predictors of the cardiovascular parameters, adjusted for hypertensive disorders of pregnancy and neonatal birth-weight *Z*-score in the index pregnancy.

The statistical software packages SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for data analysis.

Table 1 Characteristics of the study population

Characteristic	*Normal (n = 2586)*	*Pre-eclampsia (n = 66)*	*Gestational hypertension (n = 112)*	*Small-for-gestational age (n = 249)*
Maternal age (years)	32.2 (27.8 to 35.7)	30.3 (25.7 to 34.3)	32.9 (28.4 to 36.4)	31.5 (27.1 to 34.6)*
Maternal weight (kg)	78.7 (71.0 to 88.6)	85.1 (75.4 to 94.2)*	84.3 (73.6 to 95.7)*	73.0 (66.7 to 83.8)*
Maternal height (cm)	165 (161 to 169)	164 (158 to 168)	165 (162 to 169)	163 (158 to 166)*
GA at screening (weeks)	36.1 (35.9 to 36.4)	36.1 (35.7 to 36.4)	36.0 (35.8 to 36.3)	36.1 (35.9 to 36.3)
Racial origin				
Caucasian	1854 (71.7)	38 (57.6)	72 (64.3)	146 (58.6)*
Afro-Caribbean	492 (19.0)	23 (34.8)*	21 (18.8)	64 (25.7)*
South Asian	103 (4.0)	—	7 (6.3)	25 (10.0)*
East Asian	56 (2.2)	1 (1.5)	4 (3.6)	3 (1.2)
Mixed	81 (3.1)	4 (6.1)	8 (7.1)	11 (4.4)
Medical history				
Chronic hypertension	18 (0.7)	6 (9.1)*	—	1 (0.4)
Diabetes mellitus	14 (0.5)	—	1 (0.9)	—
SLE/APS	6 (0.2)	—	1 (0.9)	—
Family history of PE (mother)	71 (2.7)	5 (7.6)	8 (7.1)*	13 (5.2)
Assisted reproductive technique	74 (2.9)	3 (4.5)	2 (1.8)	5 (2.0)
Smoker	167 (6.5)	4 (6.1)	3 (2.7)	31 (12.4)*
Obstetric history				
Nulliparous	1164 (45.0)	49 (74.2)*	74 (66.1)*	161 (64.7)*
Parous				
No previous PE	1385 (53.6)	14 (21.2)*	28 (25.0)*	87 (34.9)*
Previous PE	37 (1.4)	3 (4.5)	10 (8.9)*	1 (0.4)
Interpregnancy interval (years)	2.5 (1.5 to 4.3)	3.1 (2.0 to 4.9)	2.5 (1.2 to 5.2)	3.3 (1.8 to 5.6)*
Birth-weight *Z*-score of previous pregnancy	−0.014 (−0.709 to 0.704)	0.098 (−0.482 to 1.313)	−0.106 (−1.105 to 0.315)	−0.834 (−1.553 to −0.236)*

Continuous variables are presented as median (interquartile range) and categorical variables as *n* (%). Comparisons between outcome groups were by chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables, with *post-hoc* Bonferroni correction (*$P < 0.0167$). APS, antiphospholipid syndrome; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

RESULTS

Among the 3013 women there were 66 (2.2%) who developed PE, 112 (3.7%) who developed GH, 249 (8.3%) who did not develop PE or GH but delivered SGA newborns, and 2586 (85.8%) subjects who were unaffected by PE, GH or SGA. Maternal characteristics of the study population are presented in Table 1. GA at screening was a significant predictor of cardiac output, total peripheral resistance, stroke volume, cardiac power, thoracic fluid capacity and ventricular ejection time but it was not a significant predictor of heart rate and MAP. Plots of effect estimates on the effect of maternal factors on cardiac output, stroke volume, heart rate, total peripheral resistance, MAP, cardiac power, thoracic fluid capacity and ventricular ejection time are shown in Figures 1–3. The results of the backward regression analysis for significant predictors of $\log_{10}$values of cardiovascular parameters are provided in Tables S1–S8.

DISCUSSION

Main findings of the study

The findings of this study demonstrate that in a normal pregnancy, not complicated by PE, GH or SGA, all measured maternal cardiovascular parameters are significantly affected by many maternal characteristics and variables from the obstetric and medical history.

Advancing maternal age is associated with a decrease in cardiac output and an increase in total peripheral resistance, which could be attributed to an increase in myocardial and arterial stiffness and a decrease in intrinsic heart rate[17,18]. It has previously been reported that in normal subjects after the third decade of life cardiac output decreases by about 1% per year[19]. Increasing maternal weight is associated with an increase in MAP, which can be attributed to endothelial dysfunction, insulin resistance, sympathetic nervous system overactivity and cytokines released from adipocytes[20]. Increased weight is also associated with increased cardiac output, which is mainly driven by an increase in heart rate. There is an association between obesity and alterations in heart rate variability and norepinephrine secretion, suggesting an increased sympathetic activity and reduced vagal control; this autonomic imbalance is reversible upon weight loss[21]. Increased maternal height is also associated with increased cardiac output, whereas total peripheral resistance is decreased.

In women of Afro-Caribbean, South Asian and East Asian racial origin, compared with Caucasians, cardiac output is reduced owing to a decrease in stroke volume; the heart rate is increased, which may represent a compensatory mechanism to maintain cardiac output in view of the lower stroke volume. Previous studies

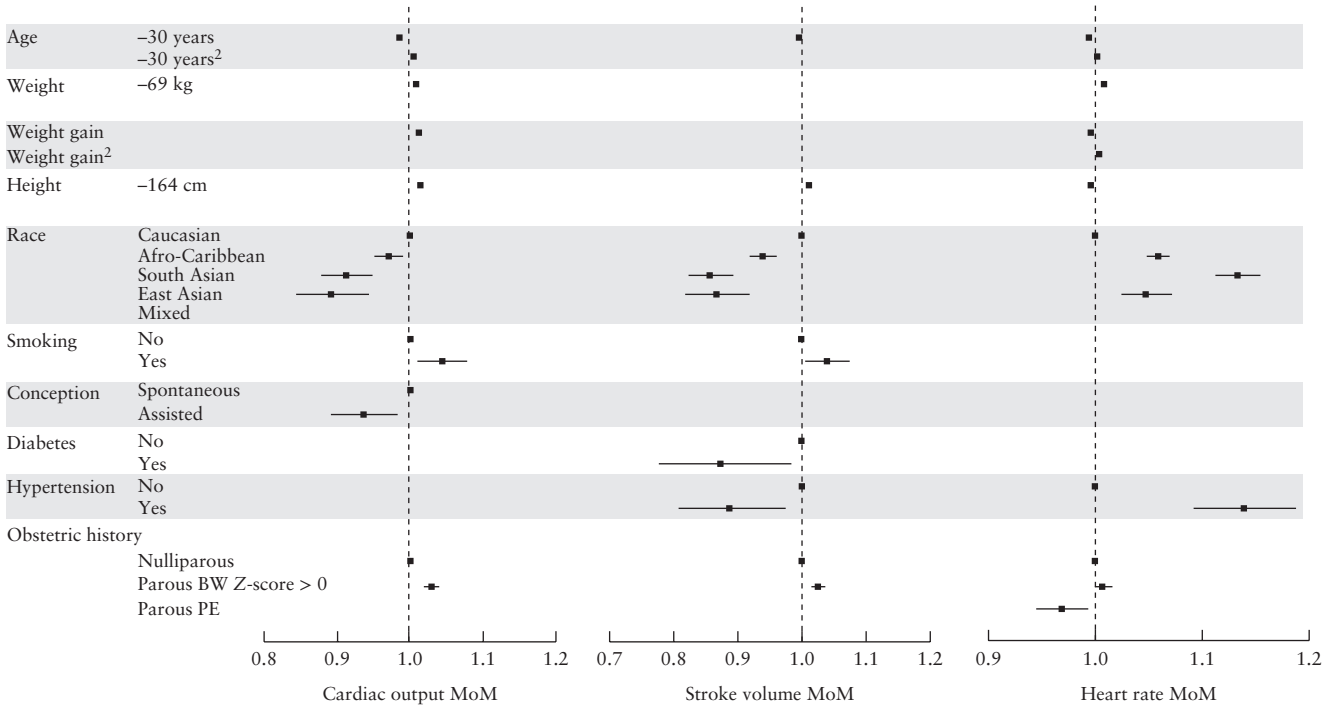

Figure 1 Plots of effect estimates of relationship between maternal characteristics and $\log_{10}$multiples of the median ($\log_{10}$MoM) values of cardiac output adjusted for gestational age at screening (GA), stroke volume adjusted for GA and heart rate in uncomplicated pregnancies without pre-eclampsia (PE), gestational hypertension or those delivering small-for-gestational-age neonates. In the case of continuous variables, maternal age was centered by subtracting 30 years, maternal weight was centered by subtracting 69 kg and maternal height was centered by subtracting 164 cm. BW, birth weight.

have reported that women of Afro-Caribbean racial origin, compared with Caucasians, have a 2–4-fold higher incidence of left ventricular hypertrophy in the presence of similar values of blood pressure[22]. Cardiovascular changes during pregnancy are thought to represent a physiological adaptation to volume overload[23], and since women of Afro-Caribbean racial origin are more susceptible to left ventricular hypertrophy they may be at increased risk of a volume-overloaded state causing functional changes in cardiac function. South and East Asians have a higher total peripheral resistance than do Caucasians. South Asians have a higher incidence of insulin resistance, obesity and cardiovascular disease, known as metabolic syndrome[24,25]. The cardiovascular effects include reduced left ventricular systolic chamber and myocardial function and increased arterial stiffness[26]; these women also have evidence of a heightened vascular inflammatory process, which may accentuate arterial stiffness, increasing vascular resistance and decreasing cardiac output due to high afterload[27]. Women of East Asian origin have a similar cardiovascular risk profile to South Asians, with higher visceral adiposity, lower lean mass and higher prevalence of insulin resistance[28].

Chronic hypertension and diabetes mellitus are associated with increased MAP and total peripheral resistance and decreased stroke volume. These conditions share common pathways, such as the sympathetic nervous system and activation of the renin–angiotensin–aldosterone system, oxidative stress, insulin resistance and inflammation with a consequent increase in arterial stiffness and vascular tone[29]. The end result is an increase in total vascular resistance with a consequent decrease in preload and stroke volume.

Smoking causes a decrease in total peripheral resistance and an increase in cardiac output owing to an increase in stroke volume. These changes may be attributed to nicotine, which can enhance the release of various neurotransmitters; some of these may contribute to the vasodilator effects of nicotine on blood vessels[30]. Nicotine can also cause catecholamine release from the adrenal medulla, which can potentiate cardiac contractility and an increase in cardiac output[31,32].

Assisted conception is associated with an increase in total peripheral resistance and a decrease in cardiac output; this is a similar pattern to that seen in PE[7,8]. It has been hypothesized that both are a result of abnormal implantation, but a previous study of ours showed that there was no significant difference in UtA-PI between *in-vitro*-fertilization and spontaneously conceived pregnancies[33]. However, in assisted conceptions there appears to be a reduction in placental volume, which may be due to a different immune response of the mother to trophoblast antigens and subsequent development of PE[34,35].

Parous compared with nulliparous women have increased cardiac output secondary to higher stroke volume and heart rate, with lower total peripheral resistance depending on the previous birth-weight *Z*-score. The effects of a past pregnancy on remodeling of the cardiovascular system have been shown to persist for

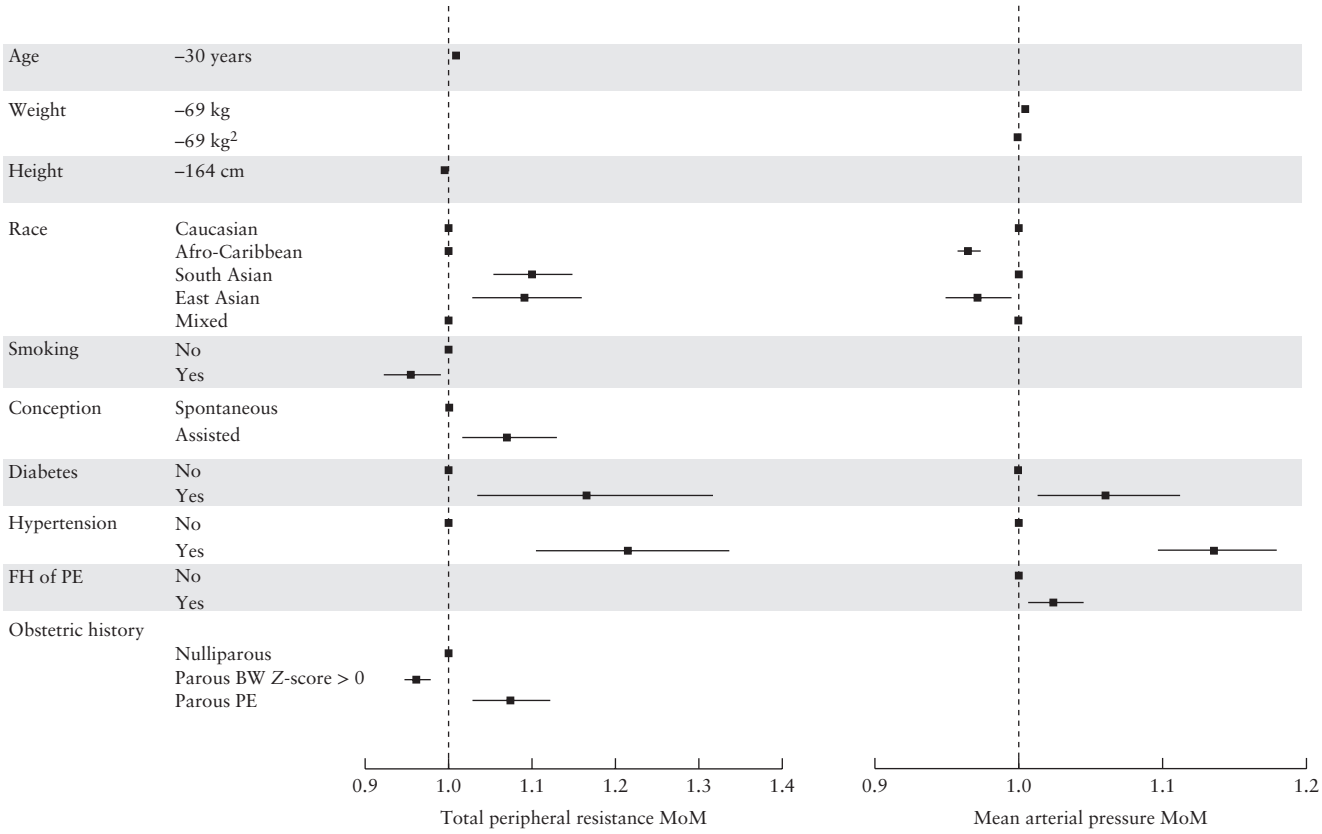

Figure 2 Plots of effect estimates of relationship between maternal characteristics and $\log_{10}$multiples of the median ($\log_{10}$MoM) values of total peripheral resistance adjusted for gestational age at screening and mean arterial pressure in uncomplicated pregnancies without pre-eclampsia (PE), gestational hypertension or those delivering small-for-gestational-age neonates. In the case of continuous variables, maternal age was centered by subtracting 30 years, maternal weight was centered by subtracting 69 kg and maternal height was centered by subtracting 164 cm. BW, birth weight; FH, family history.

many years after pregnancy[36,37]. Turan *et al.*[38] reported that with increasing parity there is a progressive increase in cardiac output, stroke volume and heart rate and a decrease in total peripheral resistance; furthermore maternal cardiac output and parity were independent predictors of birth weight.

Women with a history of previous PE, compared with nulliparous women, have a higher total peripheral resistance and lower heart rate. This may be a consequence of the residual adverse remodeling of the cardiovascular system. A family history of PE is associated with increased MAP. Studies have shown that children exposed to PE have higher systolic and diastolic blood pressure than do those of normotensive pregnancies[39]. Hypoxia, anti-angiogenesis, endothelial dysfunction and immune modifications appear to alter the epigenetic potential of offspring exposed to a PE environment *in utero*, leading to an altered vascular phenotype after birth[40].

Strengths and limitations of the study

The strengths of this study are first, prospective examination of a large population of pregnant women attending for routine care in a well-defined GA range that is currently used for third-trimester assessment of fetal growth and wellbeing; second, use of a validated and automated device by trained doctors to measure cardiovascular function; and third, application of multiple regression analysis to define the contributions and interrelationships of maternal variables that influence the measured cardiovascular parameters.

The derived MoM values are applicable only to the GA range of 35–37 weeks, and further studies are necessary to examine the effect of maternal factors on cardiovascular function at different GA ranges.

Comparison with findings of previous studies

Extensive studies in screening for trisomies and PE have established that the measured values of biophysical and biochemical markers should be expressed as MoMs after adjustment for the maternal characteristics that affect the measurements in normal pregnancies[4–7,41]. However, previous studies examining the potential value of cardiovascular parameters in screening for PE have not expressed the measured values as MoMs[8,9].

Implications for clinical practice

This study has established MoM values for a wide range of cardiovascular parameters that can now be assessed for their potential value in risk assessment and screening

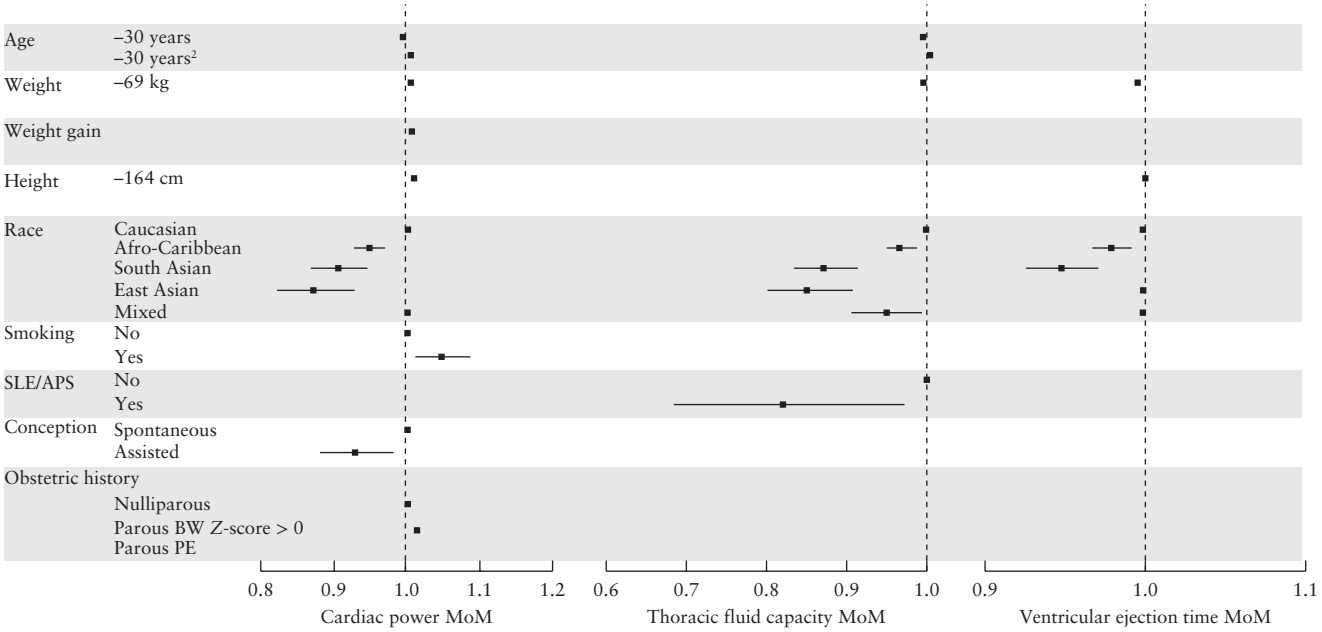

Figure 3 Plots of effect estimates of relationship between maternal characteristics and $\log_{10}$multiples of the median ($\log_{10}$MoM) values of cardiac power adjusted for gestational age at screening (GA), thoracic fluid capacity adjusted for GA and ventricular ejection time adjusted for GA in uncomplicated pregnancies without pre-eclampsia (PE), gestational hypertension or those delivering small-for-gestational-age neonates. In the case of continuous variables, maternal age was centered by subtracting 30 years, maternal weight was centered by subtracting 69 kg and maternal height was centered by subtracting 164 cm. APS, antiphospholipid syndrome; BW, birth weight; SLE, systemic lupus erythematosus.

for PE. Effective screening for PE necessitates the use of Bayes' theorem to combine the prior risk from maternal characteristics and history with a series of biophysical and biochemical markers[4–7]. In this approach, biomarkers such as cardiovascular parameters provide the additional information over that already captured in the prior model. To achieve this, the distribution of cardiac parameters should be specified conditionally on the variables included in the prior distribution. For example, increased maternal age, South Asian racial origin and diabetes mellitus are associated with an increased risk for the development of PE[42], but as demonstrated in this study in the presence of these factors peripheral resistance is increased; failure to make the appropriate adjustments to the measured peripheral resistance would inevitably overestimate its contribution to the risk of PE.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Tables S1–S8 Backward regression analysis for prediction of $\log_{10}$ cardiac output (Table S1), $\log_{10}$ total peripheral resistance (Table S2), $\log_{10}$ stroke volume (Table S3), heart rate (Table S4), $\log_{10}$ mean arterial pressure (Table S5), $\log_{10}$ cardiac power (Table S6), $\log_{10}$ thoracic fluid capacity (Table S7) and $\log_{10}$ ventricular ejection time (Table S8).