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RELATIONSHIP BETWEEN BODY MASS INDEX AND MEAN ARTERIAL PRESSURE IN NORMOTENSIVE AND CHRONIC HYPERTENSIVE PREGNANT WOMEN: A PROSPECTIVE, LONGITUDINAL STUDY

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"*Um médico que só sabe Medicina,*
nem Medicina sabe".
Abel Salazar

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Relationship between body mass index and mean arterial pressure in normotensive and chronic hypertensive pregnant women: A prospective, longitudinal study.

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Title: Relationship between body mass index and mean arterial pressure in normotensive and chronic hypertensive pregnant women: A prospective, longitudinal study.

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Abstract

Background

Being overweight is associated with both higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) during pregnancy and increased risk of gestational hypertensive disorders. The objective of this study was to determine and quantify the effect of body mass index (BMI) on mean arterial pressure (MAP) at several time points throughout pregnancy in normotensive (NT) and chronic hypertensive pregnant (HT) women.

Methods

A prospective longitudinal study was carried out in 461 singleton pregnancies (429 low-risk and 32 with chronic arterial hypertension), with measurements taken at the 1st, 2nd, and 3rd trimesters and at delivery. Linear mixed-effects regression models were used to evaluate the time-progression of BMI, SBP, DBP and MAP during pregnancy (NT *vs.* HT). The longitudinal effect of BMI on MAP, adjusted for the hypertensive status, was investigated by the same methodology.

Results

BMI consistently increased with time in both NT and HT women. In contrast, MAP decreased during the first half of pregnancy, after which it increased until the moment of delivery in both groups. A 5-unit increase in BMI was predicted to produce an increase of approximately 1 mmHg in population MAP values. This effect is independent from the time period and from hypertensive status.

Conclusions

In both NT and HT pregnant women, MAP is strongly (and significantly) influenced by increases in BMI.

Keywords: Pregnancy; Hypertension; Body mass index; Mean arterial pressure

Resumo

Introdução

O excesso de peso está associado a pressão arterial mais elevada, quer sistólica, quer diastólica, assim como a risco aumentado de doenças hipertensivas durante a gravidez. O objetivo deste estudo é determinar e quantificar o efeito do índice de massa corporal sobre o comportamento da pressão arterial média em vários momentos da gravidez, em grávidas normotensas e hipertensas crónicas.

Métodos

Um estudo longitudinal e prospectivo foi realizado em 461 gestações únicas (429 gestações de baixo risco e 32 com hipertensão arterial crónica) cujas medições foram feitas no 1º, 2º e 3º trimestres, e no momento do parto. Foram usados modelos de regressão linear de efeitos mistos para determinar o índice de massa corporal, a pressão arterial sistólica, a pressão arterial diastólica e a pressão arterial média durante a gravidez em mulheres hipertensas e normotensas. O efeito longitudinal do índice de massa corporal sobre comportamento da pressão arterial média durante a gravidez, ajustado para o estado hipertensivo (normotensas vs. hipertensas), foi avaliado pela mesma metodologia.

Resultados

O índice de massa corporal aumenta consistentemente à medida a que o tempo avança em normotensas e hipertensas. Por outro lado, a pressão arterial média diminui durante a primeira metade da gravidez e, em seguida, sobe até ao momento do parto, em ambos os grupos. Espera-se que um aumento de 5 unidades no índice de massa corporal produza um aumento de, aproximadamente, 1 mmHg nos valores da pressão arterial média na população. Este efeito é independente do tempo (fase da gravidez) e do estado hipertensivo (normotensas vs hipertensas).

Conclusões

Em ambos os grupos, quer em hipertensas, quer em normotensas, a pressão arterial média é significativamente influenciada pelo aumento do índice de massa corporal.

Palavras-chave: Gravidez, Hipertensão, Índice de Massa Corporal, Pressão Arterial Média

Abreviations

BIC - Bayesian Information Criterion

BMI - Body Mass Index

BP - Blood Pressure

CHP-MJD - Centro Hospitalar do Porto, Unidade Maternidade Júlio Dinis

CI - confidence interval

DBP - Diastolic Blood Pressure

GA - Gestational Age

HT - Hypertensive

LMEM - Linear Mixed-Effects (regression) Models

MAP - Mean Arterial Pressure

NT - Normotensive

SBP - Systolic Blood Pressure

SD - standard deviation.

Background

Chronic arterial hypertension is a serious disorder; if left untreated, it can lead to serious health outcomes, mostly affecting target organs such as the heart, brain, kidney and retina (Messerli et al., 2007). Thus, women diagnosed with hypertension who become pregnant are at an increased risk for several pregnancy complications, including superimposed preeclampsia (Perni *et al*., 2012; Seely & Ecker, 2014), foetal growth restriction (Chappel *et al*., 2008), preterm delivery (Bramham *et al*., 2014), placental abruption (Gilbert et al., 2007), and caesarean section (Bramham *et al*., 2014; Seely & Ecker, 2014). In addition, because chronic arterial hypertension affects 3-5% of pregnancies (Sibai, 2002; Lawler *et al*., 2007), it alone is a matter of concern and is increasingly encountered (Seely & Ecker, 2014). Obesity is the main risk factor contributing to this increased prevalence; its frequency is increasing among pregnant women, and it is a well-known risk factor for both adverse maternal (Gaillard *et al*., 2011a) and neonatal outcomes (Crane *et al.*, 2009; Aune *et al.*, 2014). In fact, increased adiposity during normal pregnancy has been consistently associated with the same medical complications that are associated with chronic arterial hypertension in pregnant women (as described above) (Villamor *et al.*, 2006). However, the mechanisms for these associations are not completely understood.

Several studies have examined the effects of maternal weight on blood pressure levels during different periods of normal pregnancy (Miller *et al.*, 2007; Helmreich *et al.*, 2008; Crane *et al.*, 2009; Thompson *et al.*, 2009; Mbah *et al.*, 2010; Macdonald-Wallis *et al.*, 2015). The results suggest that overweight, obesity and morbid obesity are associated with higher systolic (SBP) and diastolic blood pressure (DBP) during pregnancy and increased risks of gestational hypertensive disorders (Gaillard *et al.*, 2011a).

Nevertheless, studies that have effectively quantified the effects of weight gain on maternal blood pressure during pregnancy are lacking. It has been reasoned that additional data on the effects of increased body mass index (BMI) on mean arterial pressure (MAP) during normal pregnancy would be provided by a parallel study in women with long-term stable essential hypertension, which is a prevalent condition and a known risk factor for serious gestational disorders (Sibai, 2002; Bramham *et al*., 2014).

Based on these considerations, this study aimed to determine and quantify the effects of BMI on MAP at several time points throughout pregnancy, in normotensive (NT) and chronic hypertensive (HT) pregnant women.

Methods

The research protocol was approved by the local ethics committee (IRB protocol number: 133/10 [086-DEFI/126-CES]) of the Centro Hospitalar do Porto – Unidade Maternidade Júlio Dinis (CHP-MJD), and all of the subjects provided informed consent upon receiving an adequate explanation of the study. The methods were carried out in accordance with the approved protocol.

Study population and design

Between January 2010 and December 2012 a total of 578 pregnant Caucasian women were recruited to participant in the study. According to local pregnancy health policies, the women were referred by their family doctors to the CHP-MJD.

During their first appointment the women were observed by a senior specialist who reviewed their medical history, verified the absence of diabetes and other endocrine disorders, immune diseases, renal diseases, structural heart diseases, haematological conditions and chronic infections; gestational age (GA) was also checked by ultrasonography between 11 and 14 weeks (Robinson, 1973).

The inclusion criteria were as follows: (1) singleton pregnancy and gestational age ≤ 14 weeks, and (2) healthy status or stable chronic arterial hypertension without known target organ involvement.

The exclusion criteria were as follows: (1) patients with multiple gestations, coagulopathy, haematological pathology, diabetes, or any pregnancy-induced hypertension including preeclampsia, and (2) patients who refused to participate. Subjects were also excluded from the study if they had a preterm delivery (birth < 37^{th} gestational week), were lost to follow-up, needed antihypertensive medication, or experienced foetal death.

Chronic arterial hypertension was defined as a blood pressure of 140/90 mmHg on more than two occasions before 20 weeks of gestation or after 20 weeks of pregnancy if it persisted beyond 12 weeks postpartum. However, only women with a history of chronic arterial hypertension prior to pregnancy were enrolled in the study.

Before pregnancy, the majority of the patients required multiple medications, including thiazide, angiotensin converting enzyme inhibitor, angiotensin receptor blockers, or calcium channel blockers, to control their hypertension. After their first appointment, antihypertensive drugs were discontinued, and their blood pressure was closely monitored. Antihypertensive therapy was

restarted if a patient experienced a persistent diastolic pressure between 95 and 99 mmHg or if a systolic pressure ≥ 150 mmHg was observed at any time during their pregnancy.

Definition of time-point measurements

Anthropometric parameters and blood pressure were measured at the following four time points: 12-14 weeks, 18-22 weeks, 29-33 weeks, and delivery. Each of these time points were converted to a time scale ranging from 0 to 1. Therefore, the initial time (i.e., before pregnancy) was considered to be $time = 0$, and the time of delivery was considered to be $time = 1$.

Maternal anthropometrics

The height (cm) and weight (kg) of each subject were measured without heavy clothing and shoes at each time point. Data about maternal weight just before pregnancy was obtained through questionnaires. Pre-pregnancy body mass index (BMI) was categorized into the following three categories: lean or normal (16-24 kg/m^2), overweight (25-29 kg/m^2) and obese (30-50 kg/m^2).

Blood pressure assessment

The blood pressure (BP) was measured using an automated instrument (GE Healthcare Carescape™ V100 Vital Signs Monitor with DINAMAP Technology, Milwaukee, WI, USA); it was measured two consecutive times and averaged. Mean arterial pressure (MAP) was obtained according to the following formula:

$$MAP = \frac{(2 \times diastolic\ pressure) + systolic\ pressure}{3}$$

Prior to the measurement, each of the participants was seated and asked to relax for 5-10 minutes. A cuff (CRITIKON Blood Pressure Cuffs®, GE Healthcare, 23-33 cm, Milwaukee, WI, USA) was placed around the non-dominant upper arm at the level of the heart, with the pressure cuff bladder midline over the brachial artery. A larger cuff (32-42 cm) was used in patients who had an upper arm that exceeded 33 cm. As enrolment in our study took place during pregnancy, we were unable to measure maternal blood pressure before pregnancy.

Definition of normal pregnancy

To restrict enrolment to patients with normal course pregnancies, we excluded 117 (20.2%) pregnant women who experienced any of the following events during their pregnancies: endocrine disorders, psychiatric disorders, history of bariatric surgery, secondary hypertension,

gestational hypertension/preeclampsia, preterm delivery, foetal growth restriction, antihypertensive medication use, multiple gestation, and foetal death. After these exclusions, 461 women who had a normal pregnancy remained. Therefore, the study used basic inclusion criteria, including patients who were healthy or had stable chronic hypertension without known target organ involvement.

Efforts to address potential sources of bias

Any pregnant women who were seen by our clinical investigator during the study period were considered to be potentially eligible. The pregnancy consultations were randomly scheduled by the hospital administrative staff according to the availability of the clinical investigator (L.G-M.). The patients were consecutively recruited, and the maternal anthropometric and blood pressure measurements were taken by experienced midwives who were unaware of the study protocol. All of the pregnancies were supervised by the same physician (L.G-M.), but the inclusion of pregnancies in the study was determined by another researcher who coordinated the review of each clinical case (A.C.).

Statistical analysis

Univariate analyses included the following standard statistical methods: (1) the chi-square or Fisher's exact tests to compare frequencies from categorical variables or to study the independence between two factors; and (2) *t*-tests to assess the statistical significance of the difference between the means of two independent populations.

Time was considered a continuous variable, with values 0, 0.3, 0.5, 0.8 and 1, in the BMI model [respectively 0.3, 0.5, 0.8 and 1 in the systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and BMI effect on MAP (MAP-BMI) models]. Whilst 0 and 1 were arbitrarily chosen, the other points were proportional to the observational periods in the study; namely, before pregnancy, 12-14 weeks, 18-22 weeks, 29-33 weeks, and at delivery. Hypertension was a binary variable with normotensive status as the reference category.

Linear mixed-effects (regression) models were used with the observations grouped at the individual level (Pinheiro & Bates, 2000). The random effects in the final models were identified either at the intercept alone, or at the intercept and the time coefficient. In the final models with two random effects, the best structure for the variance-covariance matrix of the random effects was shown to be that of a general positive definite matrix. Whenver the within-group error variance function had to be modelled, the assumption of independence did not seem to be compromised. For the same individual, the errors were assumed to be independent from the

random effects; for different individuals, the errors were assumed to be independent. The normality assumptions for the random effects and errors distributions were assessed through graphical analysis; however, for the BMI-time model, the responses had to be log-transformed for the normality of the errors distribution to not be rejected, and the normality assumption within the remaining models was confirmed. Due to sample size constraints, interaction terms were only considered in the MAP-BMI model.

The final models were chosen based on the lowest Bayesian information criterion (BIC) or on the likelihood ratio test, as appropriate. All statistical analyses were carried out using R version 2.12.1 (R Development Core Team). The significance level was set at 0.05.

Results

Of the 461 women who were enrolled in the study, 429 were normotensive and 32 had chronic arterial hypertension.

Figure 1 shows the number of pregnant women at each stage of the study. The main characteristics and pregnancy outcomes are shown in Table 1. In 31.9% of the cases, caesarean section was the mode of delivery; in more than 70% of those cases, the reason for receiving a caesarean section was prior caesarean delivery, dystocia, foetal distress, or breech presentation (Table 2).

Table 3 describes the maternal anthropometrics and blood pressure during the study period. BMI consistently increased over time in both the NT and HT groups. In contrast, MAP decreased during the first half of pregnancy and then increased until the moment of delivery.

BMI model

The longitudinal model for BMI estimated a quadratic progression during pregnancy, with the same progression rate for both the NT and HT groups (Figure 2).

The model for the BMI evolution during pregnancy, for any given rescaled time t and hypertensive status h (equal to 1 for HT and 0 for NT) of the i^{th} woman, was as follows:

$$\log(BMI_i)(t,h) = \beta_0 + b_{0i} + \beta_1 h + \beta_2 t + \beta_3 t^2 + \varepsilon_i \qquad (1)$$

where the random effect b_{0i} was assumed to follow a normal distribution, and the within-group error terms ε_i were assumed to follow a multivariate (5-dimensional) normal distribution with a first-order autoregressive model for their correlation structure. The corresponding estimates are presented in Table 4. The estimates for the correlation parameter (95% CI) and the within-group standard error (95% CI) were 0.943 (0.795, 0.985) and 0.103 (0.053, 0.198), respectively. All fixed effects are multiplicative because the response was log-transformed.

The predicted BMI change during pregnancy consists of two increasing parabolic branches for each hypertensive status that are significantly different from one another; for any given time, the model predicts the hypertensive population to have a mean BMI that is significantly greater than that of the normotensive population.

SBP model

The model for SBP during pregnancy, for any given rescaled time t and hypertensive status h of the i^{th} woman, was as follows:

$$SBP_i(t,h) = (\beta_0 + b_{0i}) + \beta_1 h + (\beta_2 + b_{1i})t + \beta_3 t^2 + \beta_4 t^3 + \varepsilon_i \qquad (2)$$

where the random effects (b_{0i}, b_{1i}) were assumed to follow a bivariate normal distribution with a general positive-definite variance-covariance matrix, and the within-group error terms ε_i were assumed to follow a multivariate (4-dimensional) normal distribution. The estimates of the effects are presented in Table 4. The errors were found to have a variance function that is an exponent of the fitted values, with a coefficient (95% CI) estimated to be -0.031 (-0.037, -0.025). The correlation coefficient (95% CI) between the random effects was estimated to be -0.855 (-0.887, -0.815).

Two cubic parallel curves were obtained, one for each hypertensive status, and the SBP predictions were significantly higher for the HT group than the NT (Figure 3). For the normotensive population, the minimum and maximum expected values were 113.5 mmHg and 123.9 mmHg, respectively, and they were attained at the (rescaled) time = 0.49 and time = 0.93, respectively. For the hypertensive population, the minimum and maximum mean values (attained at the same times) were predicted to be 129.5 mmHg and 139.9 mmHg, respectively.

DBP model

The model for DBP during pregnancy was of a similar form to (2). The obtained estimates for its effects are presented in Table 4. The correlation coefficient (95% CI) between the random effects was estimated to be -0.831 (-0.882, -0.760). The variance-covariance matrix of the within group errors was diagonal with a variance function that was constant for the hypertensive and normotensive groups. When the error variance within the normotensive population was standardized to 1, the estimated variance (95% CI) of the hypertensive population was 0.691 (0.581, 0.821) times the variance prior to standardization.

Two cubic parallel curves were expected, and the DBP values were significantly higher for the HT group than the NT group (Figure 3). For the normotensive population, the minimum and maximum mean values were predicted to be 63.21 mmHg and 66.38 mmHg, respectively, and they were attained at $t = 0.64$ and $t = 1$, respectively. For the hypertensive population, the minimum and maximum mean values (attained at the same times) were predicted to be 75.16 mmHg and 78.34 mmHg, respectively.

MAP model

The model for MAP during pregnancy was again of a similar form to (2). Its estimates are presented in Table 4. The correlation coefficient (95% CI) between the two random-effects was estimated to be -0.871 (-0.828, -0.772). The variance-covariance matrix of the within group

errors was diagonal with a power variance function based on the fitted values; the variance function coefficient (95% CI) was estimated to be -1.632 (-2.206, -1.058).

For the MAP model, two cubic parallel curves, one for each hypertensive status, were predicted, and the MAP values were significantly higher in the hypertensive group than the normotensive group (Figure 4). Between 12-14 weeks, the average MAP values were 82.42 mmHg and 95.43 mmHg in the NT and HT groups, respectively. The values decreased during weeks 18-22, reaching a minimum of 80.43 mmHg and 93.44 mmHg in the NT and HT groups, respectively. After week 22, the values increased until delivery, reaching a maximum of 85.05 mmHg and 98.06 mmHg, respectively.

Adjusted BMI effect on MAP (MAP-BMI Model)

The effect of BMI on MAP was obtained by adjusting the previous MAP model for the time-dependent BMI variable. The predicted estimates for the mean and the estimates obtained for the model effects are presented in Table 4. The correlation coefficient (95% CI) between the random effects was estimated to be -0.832 (-0.875, -0.776). The variance-covariance matrix of the within group errors was diagonal with a variance function that was a power of the fitted values; the variance function coefficient (95% CI) was estimated to be -1.740 (-2.300, -1.180).

The interaction between hypertensive status and BMI was not statistically significant (p=0.275). Adjusting for BMI led to very similar conclusions regarding the time and the hypertension effects on MAP. With respect to the BMI effect, a 1-unit increase in BMI was predicted to produce an increase of 0.21 mmHg in MAP, or equivalently, a 5-unit increase in BMI was predicted to produce an increase of approximately 1 mmHg in the population MAP values (Figure 5). This effect was independent of time period and hypertensive status; that is, regardless of the time period and hypertensive status, the predicted BMI effect on MAP remained the same.

Parity was not statistically significant in any of the studied models ($p = 0.443$ for the BMI model; $p = 0.712$ for the SBP model; $p = 0.471$ for the DBP model; and $p = 0.729$ for the MAP model).

Discussion

Most of the normal increase in weight during pregnancy can be attributed to the foetus, breasts, and increases in extravascular fluid, and it causes inevitable demands on the hemodynamic balance of the pregnant. Consequently, blood pressure (BP) and maternal weight measurements play a central role in the adequate monitoring of pregnancy, during which profound metabolic and circulatory changes occur (Hermida *et al*., 2004; Miller *et al.*, 2007; Thompson *et al.*, 2009; ACOG, 2013). These cardiovascular changes begin early and include cardiac output increase, blood volume expansion, peripheral vasodilation and blood pressure reduction. Notably, half of the cardiac output increase occurs by 8 weeks of gestation, and cardiac output increases to 30-50% (1.8 L/min) above the typical baseline (i.e., in non-pregnant status) (Katz *et al*., 1978; Capeless & Clapp, 1989; van Oppen, *et al.,* 1996). As a consequence, in early pregnancy the uterus receives 3 to 6% of the cardiac output, whereas at 37-41 weeks it receives approximately 12% of the cardiac output (Flo *et al*., 2010). This increase is crucial for an adequate perfusion of the developing feto-placental unit (Robson *et al.*, 1989; Guedes-Martins *et al.*, 2014a; Guedes-Martins *et al.*, 2014b).

The results from this prospective study showed that, as in normotensive gestations (Strevens *et al.*, 2001; Gaillard *et al.*, 2011b), in chronic hypertensive pregnant women the shapes of the average SBP and MAP trajectories are characterized by a decrease until mid-pregnancy followed by an increase late in pregnancy. This pattern was much less noticeable for DBP, where little and almost no decreases in the average values were observed during pregnancy in the NT and HT groups, respectively. In addition, the differences in the SBP, DBP, and MAP trajectories between the NT and HT groups remained constant throughout pregnancy, and the trajectories temporally progress in a parallel fashion.

To our knowledge, this is the first study to quantify the effects of BMI on MAP in chronic hypertensive pregnant women. We observed that higher BMI values were associated with higher MAP values in all trimesters of pregnancy in both the NT group and the HT group. In addition, regardless of the time period and hypertensive status, the predicted effect of BMI on MAP remained the same; a 5-unit increase in BMI was predicted to produce an increase of approximately 1 mmHg in MAP.

Overall, our findings are in line with the robust association that has been found between increased adiposity and higher blood pressure in humans (Mokdad *et al*., 2003; Paradis *et al*., 2004; Gregg *et al*., 2005). Particularly, previous studies have verified the blood pressure pattern that occurs during the trimesters of pregnancy in clinically healthy pregnant women (Hermida *et*

*a*l., 2000; Hermida *et al*., 2001; Ayala *et al*., 2011) but not in a population of chronic hypertensive pregnant women.

Statistics and methodological issues

In all of the models, the two mean curves had a narrow 95% confidence interval. This suggests that most of the variability was captured by the random effects, which justifies their presence in the models. Moreover, the presence of random effects and the modelling of their variance-covariance structures competed with the correlation structure of the errors, which turned out to have a simple structure. This phenomenon is well-known in the statistical literature on mixed-effects models (Pinheiro & Bates, 2000). The fact that the best variance-covariance structure of the random effects was always a general positive definite matrix is in line with the values of the estimated correlation coefficients and variance estimates that were obtained in the various models.

In the DBP model, the estimate for the time coefficient was not statistically significant; however, this is irrelevant because the estimates of the higher-order terms were all significant.

No interactions between time and the hypertensive status of the women were considered. This was essentially due to the high-order polynomials (third order) that we found for the time variable combined with the sample size of the hypertensive group. Therefore, the predicted mean curves for the hypertensive population turned out to be a translation of the graphical mean values that were predicted for the normotensive population. However, this seemed to only negatively impact the fitting within the hypertensive population in the second evaluation period of the MAP model.

Within the MAP model, the residuals of the hypertensive group were larger than those of the normotensive group. This result was related to the strength of the model, particularly the cubic time progression that ignored the hypertensive status of the women, up to adding a constant. The authors predicted that the presence of interaction terms in the model would improve the model predictions for the hypertensive population. However, this method would be inadequate given the relatively low sample of hypertensive women. Nonetheless, the sample size imbalance between the NT and HT participants is in accordance with the prevalence of chronic hypertension during pregnancy (Sibai, 2002; Lawler *et al*., 2007).

The principal strength of this study was its prospective longitudinal design, which allowed for the assessment of data from the first trimester onwards. In addition, our analyses are based on blood pressure and weight measurements in the clinic (routine); therefore, they reflect the

patterns that occur in daily clinical practice as opposed to assessments that are made during trial conditions (Thompson *et al*., 2009).

Weight gain and hypertension

It is thought that weight gain causes hypertension (Calhoun & Grassi, 2004; Esler et al., 2008). In fact, in the general population, many cohort studies indicate that being overweight is a major risk factor for the development of hypertension and that weight loss lowers blood pressure in most hypertensive patients (Calhoun & Grassi, 2004; Messerli et al., 2007). This phenomenon has been attributed to increases in weight-related sympathetic activity, which in turn result in the down-regulation of β-adrenergic receptors; this down-regulation leads to a decreased thermogenic response and, consequently, to an increased propensity for weight gain and adiposity-related insulin resistance (Julius et al., 2000). This hypothesis has been strengthened by findings that hypertensive subjects experience a generalized decrease in β-adrenergic responsiveness, which modulates the development of obesity in hypertension (Valentini et al., 2004; Masuo et al., 2005). As a corollary, sympathetic overactivation leads to hypertension and weight gain, and the weight gain further worsens the hypertension (Calhoun & Grassi, 2004; Newsom et al., 2010). Additionally, being overweight is a cause of chronic inflammation and oxidative stress, which are involved in the pathophysiology of hypertensive disorders during pregnancy (Guedes-Martins *et al*., 2013; Guedes-Martins *et al*., 2015).

Our results suggest that preventive strategies prior to conception or adequate counselling during pregnancy should be applied to prevent obesity in reproductive-age women and to promote adequate increases in BMI during pregnancy.

Study limitations

There are several limitations to our study that should be acknowledged. First, the self-reporting of information on many covariates was generally avoided in this study, which limited the availability of detailed information about a large number of potential confounding factors, as certain adverse lifestyle-related determinants of hypertension. Second, information on maternal pre-pregnancy weight was obtained through a questionnaire; thus, it tended to be underestimated and we cannot exclude the possibility of minor misclassification. Third, the study comprised uneventful pregnancies, and thus the results cannot be extrapolated to patients with other forms of hypertensive disease during pregnancy. For the same reasons, we are not able to analyse the effect of BMI gain and the risk of gestational hypertensive disorders or any adverse pregnancy outcomes. Fourth, we were not able to measure MAP changes in relation to the distribution of

maternal fat, which is more related to endothelial dysfunction, although BMI is highly correlated with visceral fat (Sidney *et al.*, 1999). Fifth, the generalizability of our investigation is also limited because our participants were all White women. Sixth, because we did not assess pregnancies with adverse outcomes, the clinical relevance of our findings remains uncertain.

Conclusions

This study provides evidence that, in normotensive and chronic hypertensive pregnant women, MAP is strongly influenced by increases in BMI starting in the first trimester and lasting until delivery.

Abbreviations

BIC, Bayesian information criterion; BMI, body mass index; BP, blood pressure; CHP-MJD, Centro Hospitalar do Porto – Unidade Maternidade Júlio Dinis; CI, confidence interval; DBP, diastolic blood pressure; GA, gestational age; HT, chronic arterial hypertension; MAP, mean arterial pressure; NT, normotensive; SBP, systolic blood pressure; SD, standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

L.G-M. designed the study, performed data collection, analysed the data, and composed the manuscript. M.C. contributed to data collection, analysed the data, and composed the manuscript; C.S and A.R.G. performed all statistical analyses and contributed to the critical revision of the manuscript; A.C. coordinated the review of clinical cases and organization of study groups; J.S. designed the study and analysed the data; F.M. and H.A. analysed the data, and contributed to the critical revision of the manuscript. All authors contributed to the data interpretation and the final version of the manuscript, and they all approved the final manuscript version.

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FIGURES AND TABLES

Figure legends

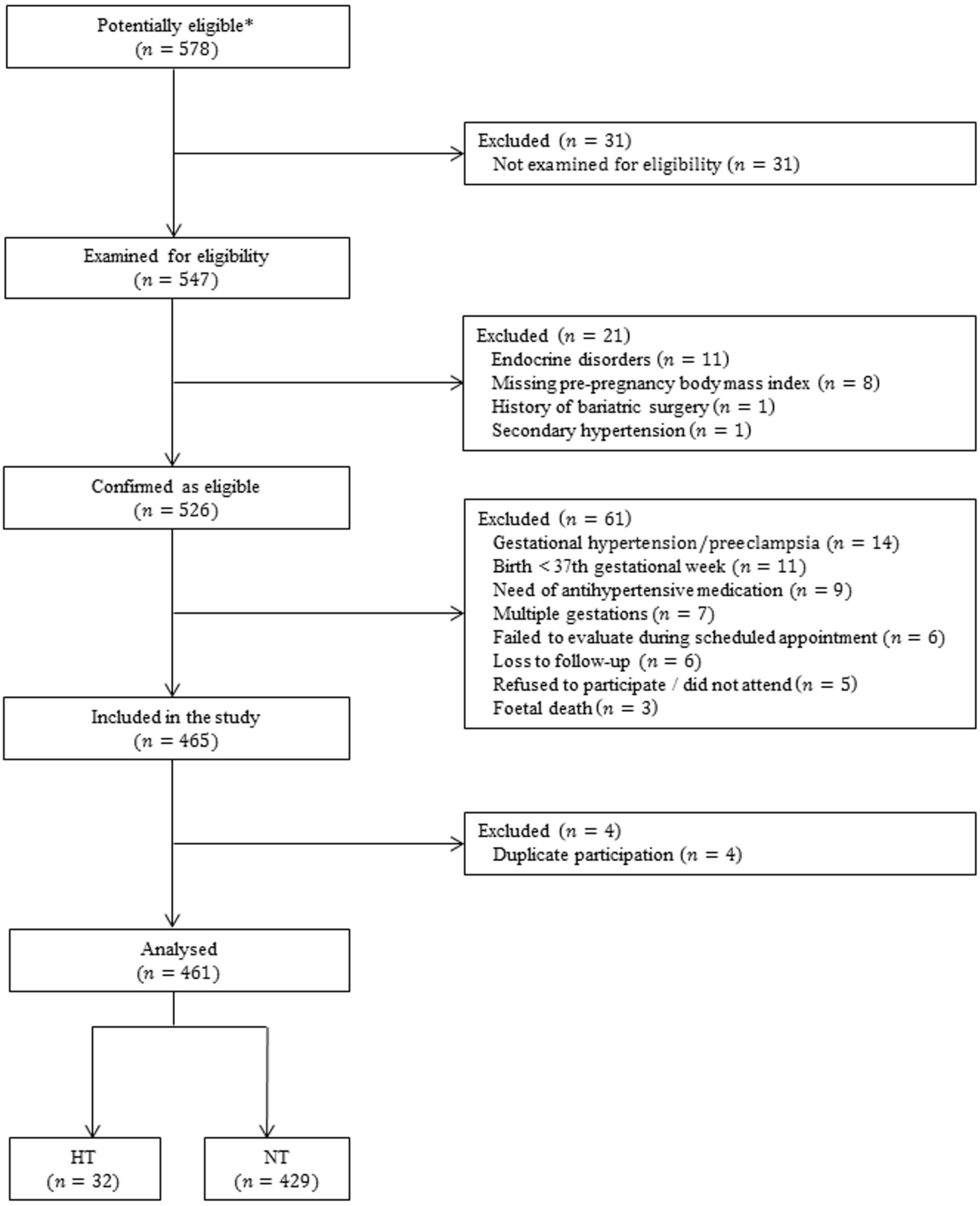

Figure 1. Study flowchart: number of pregnant women at each stage of the study. * Any pregnant women who were seen by our clinical investigator during the study period were considered to be potentially eligible.

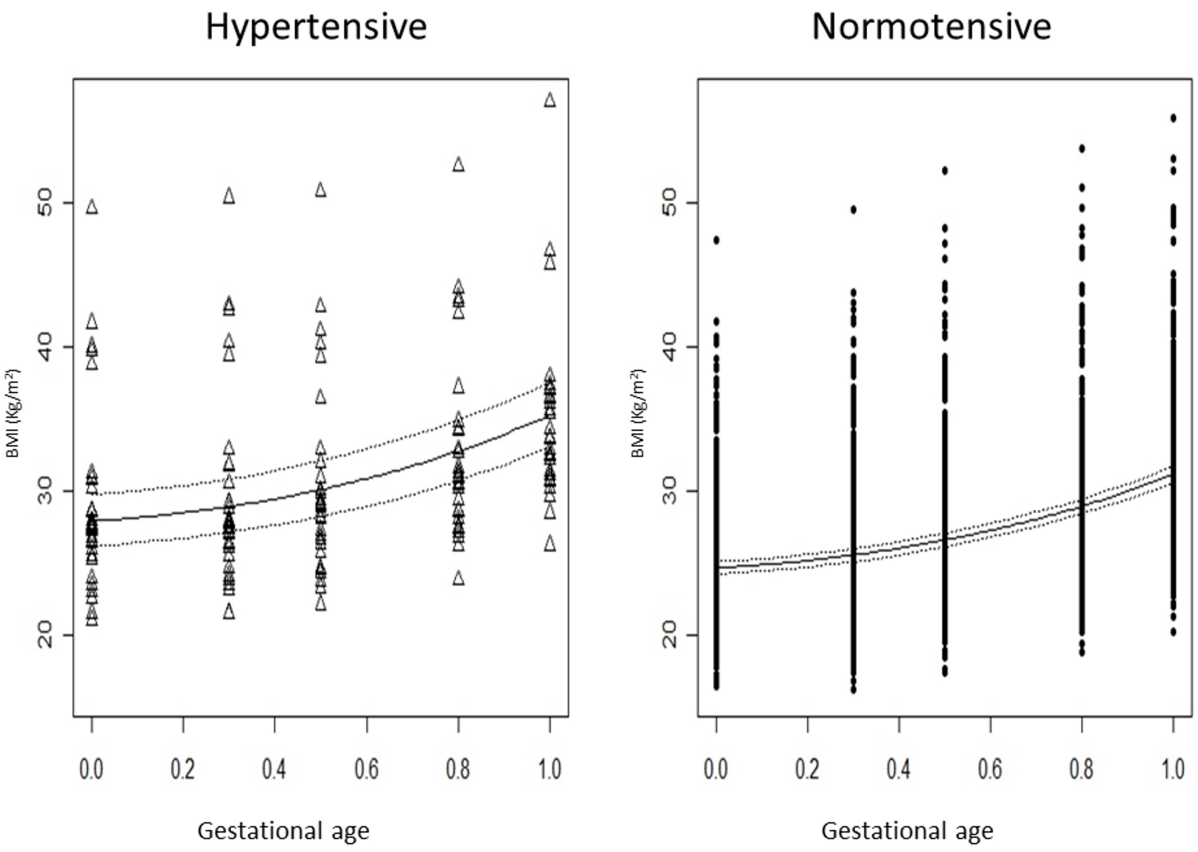

Figure 2. Expected body mass index (BMI) over time in the hypertensive (triangles) and normotensive (circles) women. The 95% confidence intervals for the respective predictions are indicated (dashed lines).

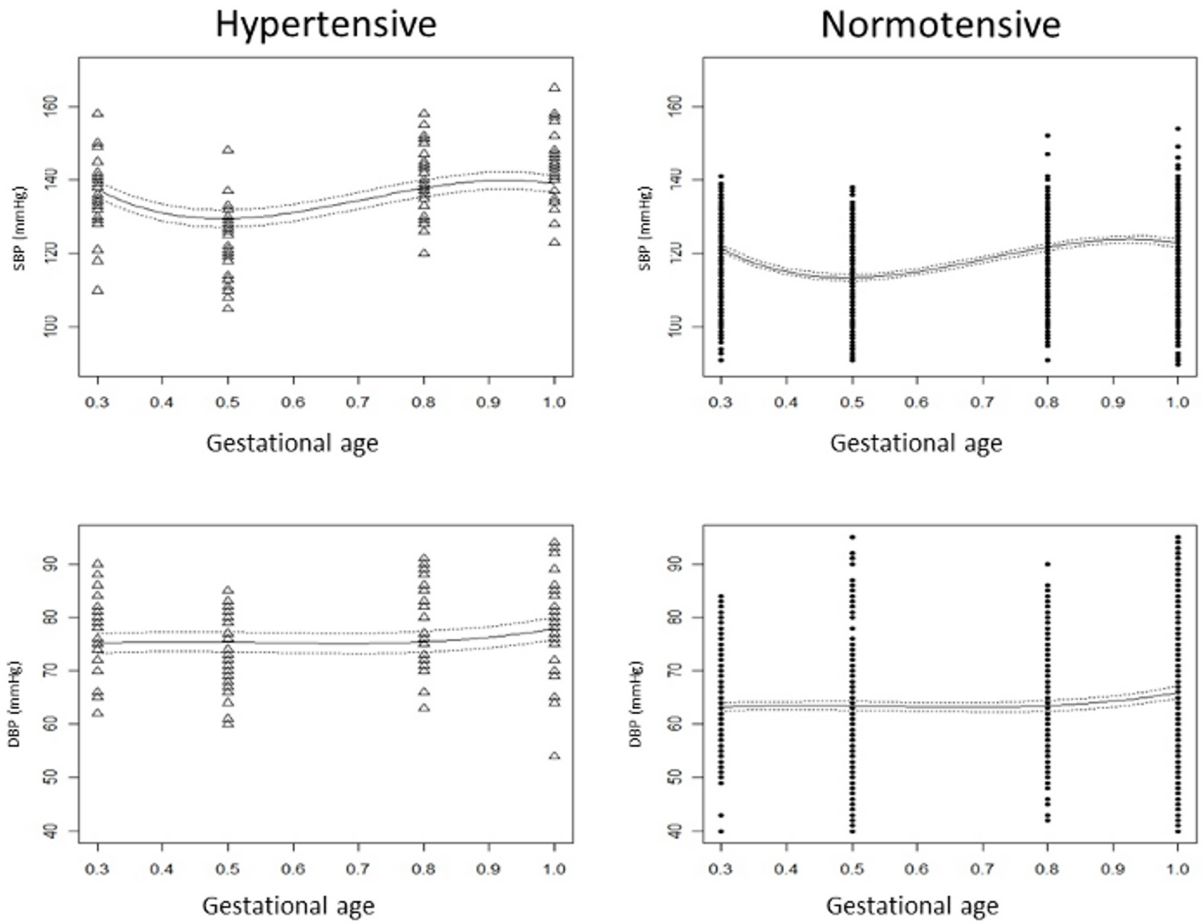

Figure 3. Expected systolic (SBP) and diastolic blood pressure (DBP) over time in the hypertensive and normotensive women. The 95% confidence intervals for the respective predictions are indicated (dashed lines).

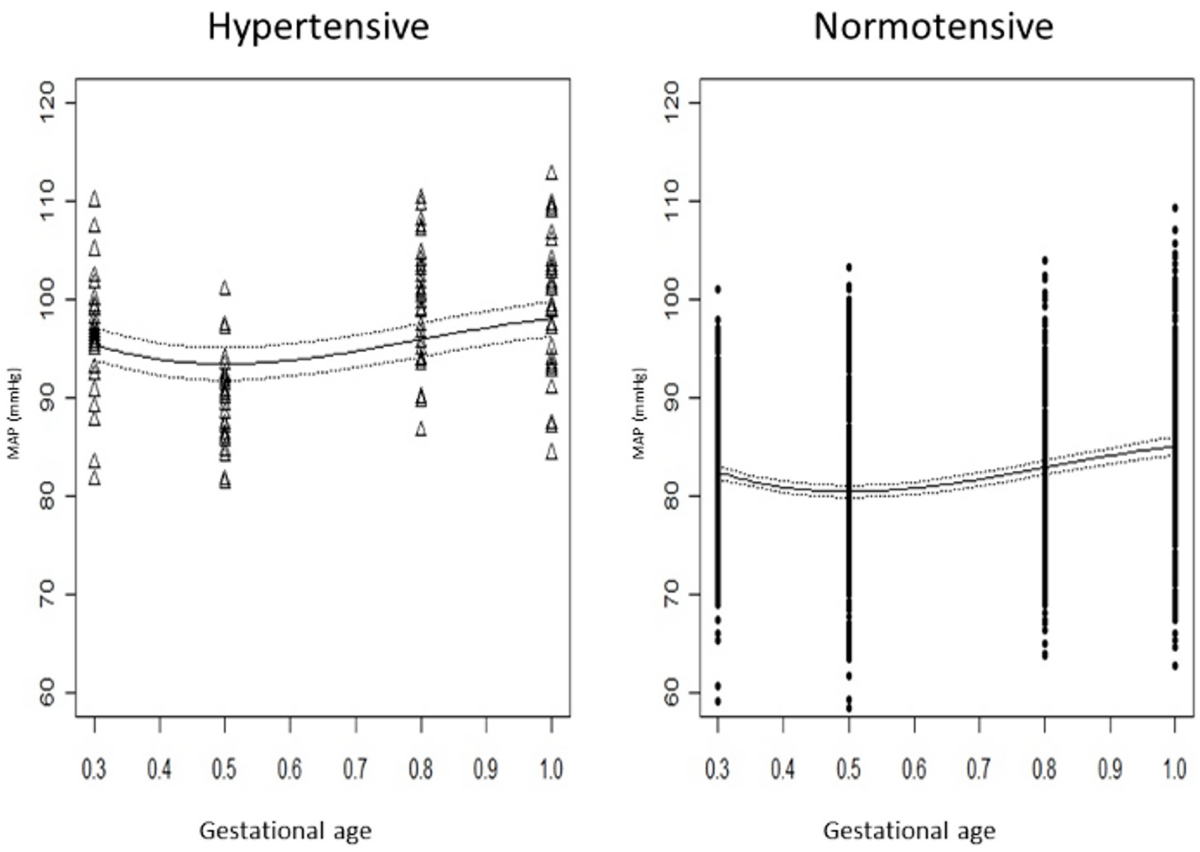

Figure 4. Expected mean arterial pressure (MAP) over time in the hypertensive (triangles) and normotensive (circles) women. The 95% confidence intervals for the respective predictions are indicated (dashed lines).

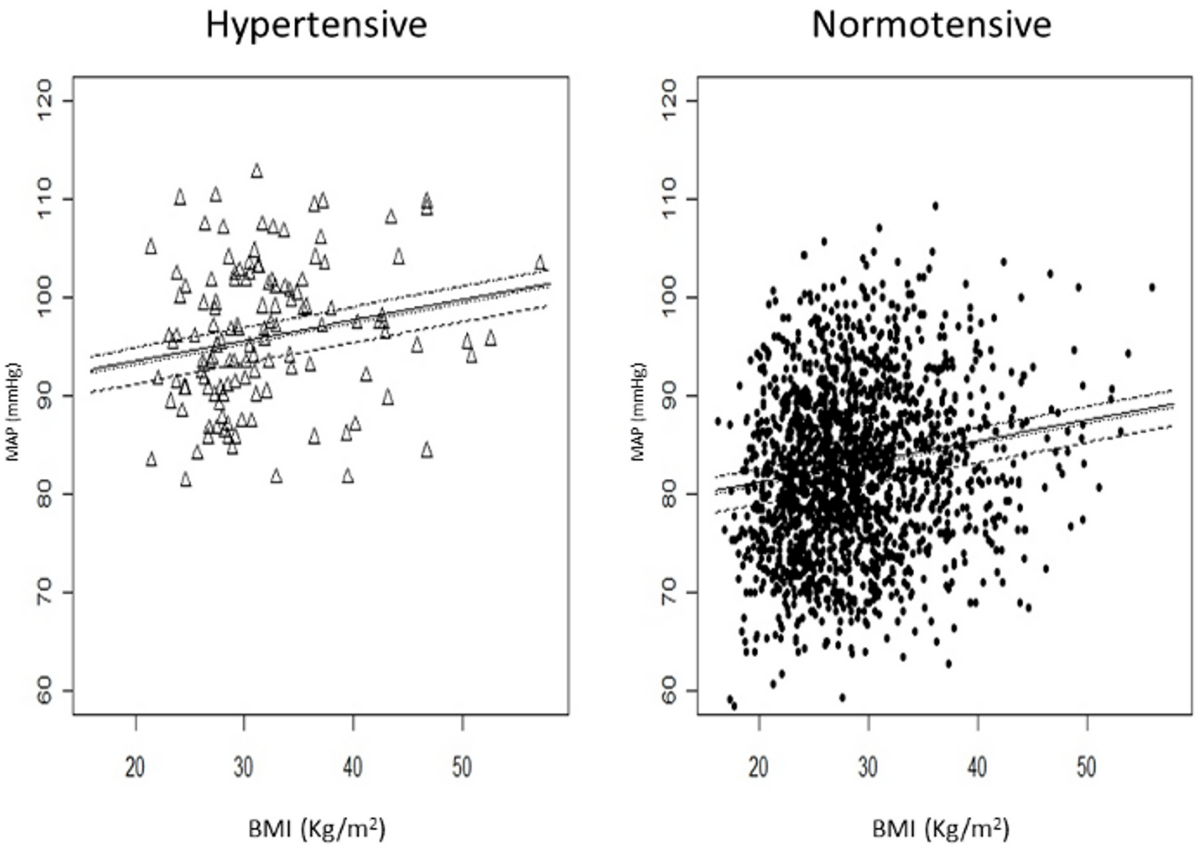

Figure 5. Expected effects of body mass index on mean arterial pressure, at different time points during pregnancy, in the hypertensive and normotensive pregnant women. Solid line, 12-14 weeks; dashed line, 18-22 weeks; dotted line, 29-33 weeks; dashed-dotted line, at delivery. The effect is always the same, geometrically reflected on a unique slope, regardless of the time period and hypertensive status.

Tables

Table 1. Demographic characteristics and pregnancy outcomes of the 461 women included in the analysis.

				Normotensive	Hypertensive		BMI (kg/m^2)			
		n (%)	p-value[1]	n=429	n=32	p-value[2]	16-24	25-29	30-50	p-value[3]
Age years [years (%)]	16-24	102 (22%)	<0.001	102 (24%)	0	<0.001	66 (26%)	20 (17%)	16 (18%)	0.047
	25-35	303 (66%)		285 (66%)	18 (56%)		164 (65%)	78 (66%)	61 (67%)	
	36-43	56 (12%)		42 (10%)	14 (44%)		22 (9%)	20 (17%)	14 (15%)	
Parity [n (%)]	0	238 (52%)	0.485	226 (53%)	12 (38%)	0.140	135 (54%)	54 (46%)	49 (54%)	0.335
	≥1	223 (48%)		203 (47%)	20 (62%)		117 (46%)	64 (54%)	42 (46%)	
Gestational age at delivery, *weeks* [mean (SD)]	39.22 (1.20)	-	NA	39.24 (1.17)	38.93 (1.68)	0.308	39.21 (1.18)	39.20 (1.28)	39.25 (1.22)	0.960
Foetal sex [n (%)]	Female	245 (53%)	0.177	229 (53%)	16 (50%)	0.852	129 (51%)	62 (53%)	54 (59%)	0.405
	Male	216 (47%)		200 (47%)	16 (50%)		123 (49%)	56 (47%)	37 (41%)	
Birth weight at delivery, *g* [mean (SD)]	3128 (334)	-	NA	3136 (329)	3007 (379)	0.070	3116 (350)	3167 (321)	3108 (301)	0.042
Apgar Score Index at 5’	<7	0	NA	0 (0%)	0 (0%)	<0.001	0	0	0	<0.001
	7 - 10	461 (100%)		429 (100%)	32 (100%)		252 (100%)	118 (100%)	91 (100%)	

[1] p - tested equality of population frequencies amongst the different categories of a variable; [2] p - tested homogeneity of the proportions between HT (hypertensive) and NT (normotensive); [3] p - tested homogeneity of the proportions between normal weight, overweight and obese; BMI, body mass index; SD, standard deviation.

Table 2. Indication for caesarean sections (**n = 147**) in the study sample.

		Caesarean deliveries (%)*		
		All (%) n=147	Normotensive (%) n=135**	Hypertensive (%) n=12†
Primary	Dystocia	29 (20)	27 (20)	2 (17)
	Non-reassuring foetal heart rate	21 (14)	19 (14)	2 (17)
	Abnormal presentation	18 (12)	17 (13)	1 (8)
	Unsuccessful trial of forceps or vacuum	14 (10)	13 (10)	1 (8)
Repeat	No VBAC attempt	40 (27)	36 (27)	4 (33)
	Failed VBAC	16 (11)	15 (11)	1 (8)
	Unsuccessful trial of forceps or vacuum	9 (6)	8 (6)	1 (8)

Data are shown as absolute (relative, %) frequencies; VBAC, vaginal birth after caesarean; The sums of the relative frequencies in the categories were 101% and 99%† due to rounding.

Table 3. Description of maternal anthropometrics and blood pressure at each study period.

	Period	Normotensive	Hypertensive
Weight kg, mean (SD)	Pre-pregnancy	64.09 (12.65)	75.17 (17.06)
	12-14 weeks	65.94 (13.03)	76.83 (17.67)
	18-22 weeks	69.82 (13.69)	78.69 (16.96)
	29-33weeks	75.92 (13.99)	85.03 (16.34)
	At delivery	80.96 (14.12)	92.95 (16.93)
BMI kg/m^2, mean (SD)	Pre-pregnancy	25.10 (5.18)	28.76 (6.54)
	12-14 weeks	25.83 (5.38)	29.40 (6.79)
	18-22 weeks	27.35 (5.66)	30.12 (6.52)
	29-33weeks	29.75 (5.86)	32.56 (6.39)
	At delivery	31.73 (5.98)	35.59 (6.59)
SBP mmHg, mean (SD)	Pre-pregnancy	-	-
	12-14 weeks	119.79 (10.62)	136.22 (9.36)
	18-22 weeks	114.37 (10.28)	123.65 (9.29)
	29-33weeks	119.91 (11.03)	140.81 (8.52)
	At delivery	121.50 (11.66)	143.75 (8.84)
DBP mmHg, mean (SD)	Pre-pregnancy	-	-
	12-14 weeks	63.05 (8.15)	76.09 (6.89)
	18-22 weeks	64.09 (11.44)	72.62 (6.84)
	29-33weeks	62.93 (10.85)	78.94 (8.05)
	At delivery	66.13 (11.54)	76.88 (9.21)
MAP mmHg, mean (SD)	Pre-pregnancy	-	-
	12-14 weeks	81.96 (6.75)	96.14 (6.01)
	18-22 weeks	80.85 (8.52)	86.64 (4.45)
	29-33weeks	81.93 (8.28)	99.56 (6.45)
	At delivery	84.59 (8.82)	99.16 (6.91)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SD, standard deviation.

Table 4. Estimates for the fixed and random effects identified by the (longitudinal) mixed-effects model for body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and adjusted BMI effect on MAP (MAP-BMI), in normotensive (NT) and chronic hypertensive (HT) women. The NT women were designated as the reference category.

	Fixed Effects	**Coefficient**	**Standard Error**	**p-value**	**Random effects**	**Standard Deviation (95% CI)**
BMI	Intercept	3.206	0.009	<0.001	Intercept	0.158 (0.117, 0.212)
	HT (*vs.* NT)	0.124	0.034	<0.001	-	-
	Time	0.067	0.006	<0.001	-	-
	$(Time)^2$	0.167	0.006	<0.001	-	-
SBP	Intercept	183.644	3.692	<0.001	Intercept	11.237 (10.058, 12.553)
	HT (*vs.* NT)	16.034	1.166	<0.001	-	-
	Time	-346.487	20.000	<0.001	Time	18.351 (16.601, 20.285)
	$(Time)^2$	539.023	32.389	<0.001	-	-
	$(Time)^3$	-253.282	16.192	<0.001	-	-
DBP	Intercept	57.967	3.905	<0.001	Intercept	7.036 (5.702, 8.683)
	HT (*vs.* NT)	11.954	0.974	<0.001	-	-
	Time	32.958	21.255	0.121	Time	15.327 (13.516, 17.380)
	$(Time)^2$	-63.105	35.012	0.072	-	-
	$(Time)^3$	38.120	17.863	0.033	-	-
MAP	Intercept	96.181	2.902	<0.001	Intercept	6.719 (5.802, 7.780)
	HT (*vs.* NT)	13.014	0.851	<0.001	-	-
	Time	-74.081	15.754	<0.001	Time	12.745 (11.443, 14.196)
	$(Time)^2$	107.357	25.840	<0.001	-	-
	$(Time)^3$	-44.409	13.116	0.001	-	-
MAP-BMI	Intercept	91.209	3.026	<0.001	Intercept	6.509 (5.604, 7.562)
	HT (*vs.* NT)	12.283	0.837	<0.001	-	-
	BMI	0.210	0.039	<0.001	-	-
	Time	-75.634	15.635	<0.001	Time	12.713 (11.422, 14.150)
	$(Time)^2$	108.038	25.629	<0.001	-	-
	$(Time)^3$	-45.221	13.004	0.001	-	-

APPENDIX

Uterine artery impedance during puerperium in normotensive and chronic hypertensive pregnant women

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MATERNAL-FETAL MEDICINE

Uterine artery impedance during puerperium in normotensive and chronic hypertensive pregnant women

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Abstract
Purpose The present study compared the Doppler flow pulsatility indices (PI) in the uterine arteries (UtA) during the puerperium between healthy women and those with stage-1 essential hypertension who had uncomplicated pregnancies and delivered by elective caesarean section. The change in the mean arterial pressure (MAP) and body mass index (BMI) over time was also assessed.
Methods A longitudinal and prospective study was performed in singleton pregnancies of 28 normotensive (NT) and 24 hypertensive (HT) women. The UtA-PI was measured immediately before caesarean section (time 0) and at 1 week (time 1) and 4 weeks (time 2) postpartum. The presence or absence of early diastolic notches was recorded. The change in the MAP, BMI, and UtA-PI over time and between the two populations was modelled through multivariate linear regression using the generalised least squares.
Results In both groups, the UtA-PI significantly increased from time 0 to time 1 ($p < 0.05$) and time 2 ($p < 0.05$). Stage-1 hypertension did not change the trend but did increase the UtA-PI magnitude ($p < 0.05$). The presence of uterine artery notching increased over time, from 6 to 98 %, in both groups ($p < 0.001$); however, in the HT group, at time 1, the majority of women exhibited positive notching [92 % (HT) vs 57 % (NT), $p = 0.013$].
Conclusions Chronic stage-1 hypertensive women with normal pregnancy outcomes exhibited a progressively increasing postpartum UtA impedance. This trend also occurred in normotensive women, albeit at a significantly lower magnitude.

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Keywords Doppler ultrasound · Uterine artery · Postpartum · Hypertension · Pulsatility index

Introduction

Soon after a pregnancy is established, there is a progressive increase in the blood demand in the pelvic canal to meet the requirements of the growing uterus and foetus. The uterine artery (UtA) in particular undergoes important functional changes that can be assessed using computerised analysis of its blood velocity spectrum measured by Doppler ultrasound. This procedure has expanded quite rapidly in obstetrics recently due to its non-invasive nature and the relative simplicity of currently available devices and techniques. Moreover, the technique enables quantitative measurement of the impedance as the pulsatility (PI) and resistance (RI) indices, which are important for functional categorization of the uterine artery. The PI is considered to describe the shape of the velocity waveform much better than other indices [1].

The UtA impedance has been measured in reproductive-age women before pregnancy [2, 3], during pregnancy [1, 4], and at delivery [5, 6]. In non-pregnant women, the uterine artery flow velocity during systole rapidly rises and falls, and is followed by a notch during early diastole [2]; during the menstrual cycle, the impedance decreases during the luteal phase before increasing as menstruation approached in parallel with the increasing plasma progesterone and oestradiol concentrations, which rise as implantation nears [3, 7].

During pregnancy in healthy women, the uterine artery blood volume increases and is paralleled by a progressive decrease in the blood flow impedance beginning at early gestation [4] and lasting throughout the remaining pregnancy until term [1]. This is thought to result from the impressive structural changes at the placental bed. The placenta-derived trophoblastic cells migrate across the decidua layer to the inner third of the myometrium to reach the maternal spiral arteries, which are the distal branches of the uterine artery; the trophoblasts then invade the vascular walls and replace most of the muscular and endothelial cells [8, 9]. This migration renders the uterine arteries low-impedance/high-capacitance vessels, and the PI decreases. In contrast, a sustained or increased UtA-PI is thought to have prognostic value for the development of uterine disorders such as preeclampsia (PE) [10, 11] and placental abruption [12, 13], and is correlated with adverse perinatal outcomes [14–16].

Upon delivery, the hemodynamic features reverse; the cardiac output and heart rate fall, and in most studies, the uterine artery impedance increases due to a sudden drop in nutritional demand. In fact, increased vascular resistance reportedly begins very early postpartum and progresses thereafter [17–19]; the UtA protodiastolic notch also reappears in tandem in a progressive fashion [19]. In contrast to the wealth of studies performed during pregnancy, the changes in the pelvic circulation puerperium have received much less attention. However, serious pathological conditions can arise during this period including haemorrhage, anaemia, infection, disabling pain, and unexpected PE. Preeclampsia is particularly important because it is first recognised at the postpartum period in approximately 5 % of cases, and its morbidity and mortality may be considerable [20].

Thus, it is important to have a better understanding of the changing pelvic features, circulatory or otherwise, during this postpartum period. Apart from obtaining data from normotensive women, we reasoned that additional information on the uterine artery performance during pregnancy could be provided by a parallel study in women with chronic stable hypertension because hypertension is a prevalent condition and a known risk factor for serious disorders of the pregnancy, including PE [21–23]. Therefore, in the present study, we compared the Doppler flow impedance in the uterine arteries postpartum in healthy, normotensive women to those with stage-1 essential hypertension who had uncomplicated pregnancies and a normal puerperium period. To exclude the expected confounder effect of the delivery method on the postpartum uterine artery impedance behaviour, only women undergoing elective caesarean section were included.

Materials and methods

Subjects

This study was approved by the local ethics committee of Centro Hospitalar do Porto-Unidade Maternidade Júlio Dinis, and all subjects provided informed consent [Ref. 150-13(096-DEFI/122-CES)].

From January 2010 to December 2012, women with singleton pregnancies at term and scheduled for elective caesarean section (due to foetal breech presentation, suspected cephalopelvic disproportion, or previous caesarean section) were recruited and allocated into two groups. The first group included healthy women who had uneventful pregnancies. The second comprised women with a history of chronic arterial hypertension prior to pregnancy. Acceptable medication in both groups was folic acid, vitamin, and iron supplements. Additionally, all hypertensive pregnant women received acetylsalicylic acid (100 mg per day) and methyldopa (500–750 mg divided into two to three doses per day). Oral acetylsalicylic acid was

administered starting at 6–14 weeks of gestation and continued until the day of delivery, according to our institutional protocol for managing chronic hypertensive pregnant women. Before pregnancy, the majority of patients required multiple medications to control their hypertension including thiazide, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, or calcium channel blockers. After the first appointment, antihypertensive drugs were discontinued, and the blood pressure response was closely monitored. Antihypertensive therapy was reinstituted if persistent diastolic pressures of 95–99 mmHg or a systolic pressure $\geq$150 mmHg was observed at any time during pregnancy.

Gestational age was determined by ultrasonography between 11 and 14 weeks. Biometric data, blood pressure, uterine artery Doppler flow analysis, and the body mass index (BMI) were measured at three time points: immediately before caesarean section (Time 0), and 1 (Time 1) and 4 (Time 2) weeks after delivery. On the day of caesarean section, all women were observed by a senior specialist who reviewed the patient's history and verified the absence of diabetes and other endocrine disorders, immune diseases, renal, structural heart diseases, haematological conditions, and chronic infections. Patients in labour, those with ruptured membranes, those with multiple foetuses, and those receiving β-tocolytic drugs, as well as those who had reported per-operative complications were excluded. Foetal disorders or newborn abnormalities, verified by a neonatologist at birth and 1 month later, were additional criteria for exclusion.

Blood pressure assessment

The blood pressure (BP) was measured immediately before Doppler flow assessment using an automated instrument (GE Healthcare Carescape™ V100 Vital Signs Monitor with DINAMAP Blood Pressure) three consecutive times and averaged. Blood pressure was expressed as the mean arterial pressure (MAP) according to the formula:

$$\text{MAP} = \frac{(2 \times \text{diastolic pressure}) + \text{systolic pressure}}{3}.$$

Doppler flow assessment

The Doppler flow evaluation of right and left UtA was performed at the three time points employing a 4 MHz convex transabdominal probe at baseline (Time 0) and a transvaginal transducer at Times 1 and 2 (GE Healthcare Technologies, Voluson 730 Pro, USA). Nursing mothers were required to abstain from breastfeeding for at least 30 min prior to examination.

For the UtA transabdominal evaluation (Time 0), the probe was placed on the lower abdominal quadrants and angled medially, and colour Doppler imaging was used to localise the UtA as it crossed over the external iliac artery. In all cases, an angle less than 30° was assured before the pulsed Doppler probe was placed over the entire vessel width. Angle correction was then applied, and the signal was updated until three similar consecutive waveforms were observed. The left and right uterine artery pulsatility (UtA-PI) indices were calculated using the device software. For the UtA transvaginal assessment (Times 1 and 2), a sagittal section of the uterus was obtained, and the cervical canal and internal cervical ostium were identified. The transducer was gently tilted from side to side, and colour flow mapping was used to identify each uterine artery alongside the cervix and uterus at the level of the internal ostium. Pulsed wave Doppler was used with the sampling gate set at 2 mm to image the entire vessel and ensure that the angle of insonation was <30°. Finally, the mean UtA-PI of the left and right arteries was calculated (Fig. 1).

The presence or absence of a bilateral early protodiastolic notch in the UtA was noted. A positive notch was defined as a persistent decrease in the blood flow velocity during early diastole below the diastolic peak velocity in at least one UtA Doppler ultrasound spectrum. Absence of the notch was defined by its bilateral absence.

All measurements were made by a single investigator with extensive experience in Doppler ultrasound to avoid inter-observer variability. Intra-observer reliability was estimated from two consecutive readings among the first 40 PI recordings in the UtA (20 transabdominal and 20 transvaginal).

Statistical analysis

Univariate data analysis was performed using the Chi square test or Fisher's test as appropriate to determine independence amongst two factors, the *t* test for the difference in means from two independent populations, and one-way analysis of variance for repeated measurements. Tukey's multiple comparisons test was used to assess statistically significant differences across more than two means in paired populations.

The change in the UtA-PI, MAP, and BMI over time in each group was modelled through multiple linear regression. The generalised least squares with maximum likelihood estimation method was applied to correlated and heteroscedastic errors following a normal distribution. For each dependent variable, the best model was chosen based on the lowest value of the Bayesian Information Criterion (BIC).

For each woman with a hypertensive status *h* (equal to 1 for hypertensive women and 0 otherwise), at continuous time *t* representing the number of weeks after labour, the MAP was modelled by the following equation:

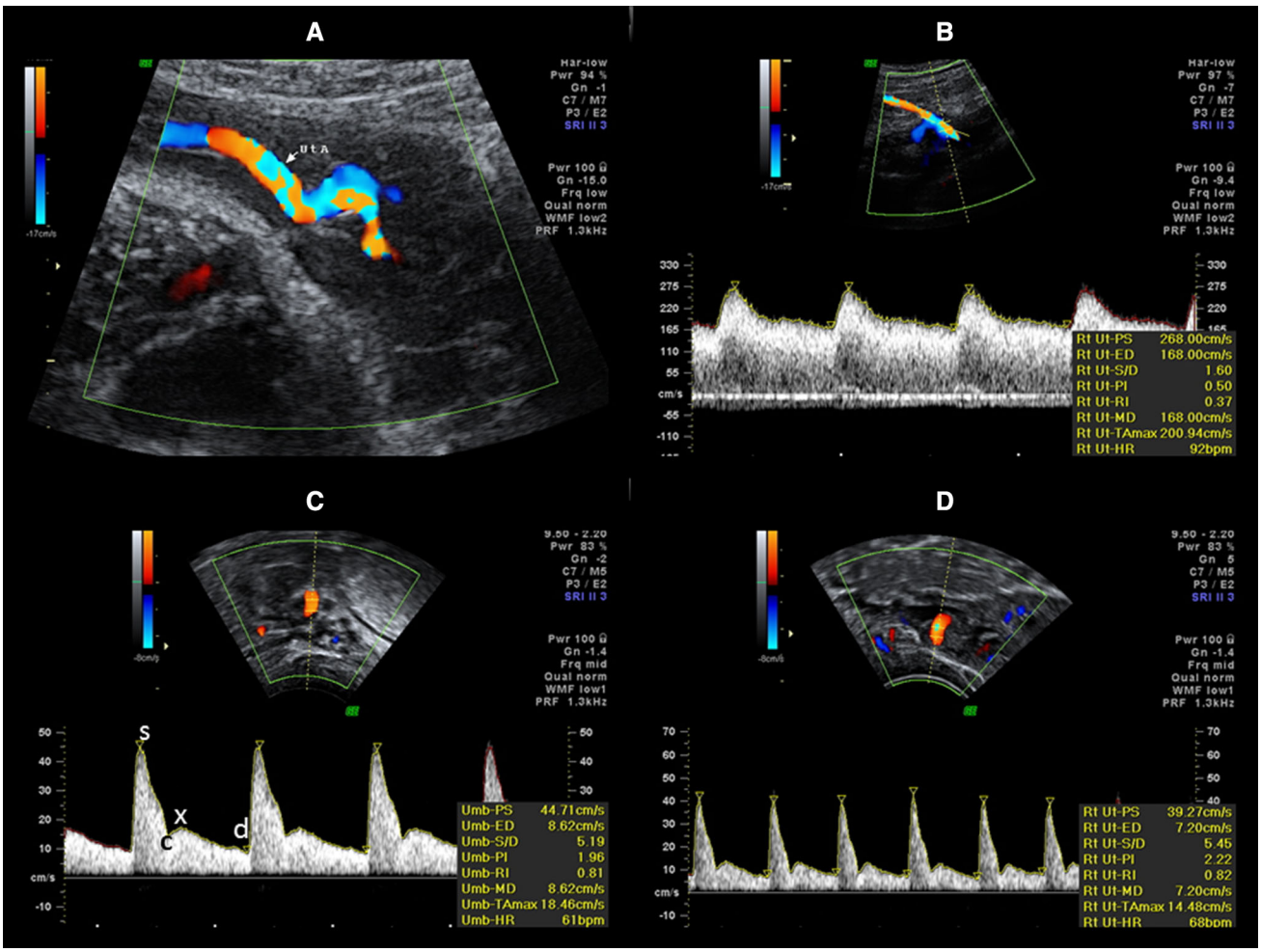

Fig. 1 **a** Uterine artery (UtA) depicted in colour flow map. Typical Doppler shift spectra recorded at time 0 (**b**), 1 week (**c**), and 4 weeks (**d**) after delivery. In **b** waveforms, the velocity gradually decreased from its systolic peak, and a continuous forward flow was observed during diastole. In **c** and **d**, the waveforms show a notch before beginning continuous diastole forward flow. Pulsatility index (PI), the measure of impedance of blood flow distal to the sampling point, was calculated according to the formula: $\mathrm{PI} = \frac{(s-d)}{\mathrm{mean}}$, where s is the peak systolic, d is the minimum end-diastolic, and *mean* is the average maximum Doppler shift frequency over the cardiac cycle. c early diastolic, x maximum diastolic frequency

$$\mathrm{MAP}(h,t) = \beta_0(h) + \beta_1(h)t + \varepsilon. \quad (1)$$

Both the intercept and the time-slope coefficient are linear functions of the hypertensive status, and ε represents the errors of the model. The errors correlation structure had compound symmetry within each hypertensive status. Time was coded as 0, 1, or 4, and was considered a continuous variable to reflect the real time differences between the three evaluation periods.

For BMI, the best fitted model was as follows:

$$\log(\mathrm{BMI}(h,t)) = \beta_0(h) + \beta_2 t + \varepsilon \quad (2)$$

with the BMI logarithm linear in both hypertensive status and time.

The model obtained for the pulsatility index had an identical structure to model (2). However, the errors from model (2) had an identical compound symmetry structure within each individual and different variances depending on the hypertensive status, but the errors correlation structure in the PI model had a compound symmetry within each hypertensive status and different error variances according to the hypertensive status.

The intraclass correlation coefficient (ICC) and 95 % confidence intervals were calculated using a two-way mixed-effects model with absolute agreement. The reliability coefficient, which is the difference value exceeded by only 5 % of measurement pairs on the same subject, was calculated as 1.96 times the standard deviation of the difference between pairs of repeated measurements.

Statistical analyses were performed using the R language and software environment for statistical computation, version 3.0.11 [24]. The significance level was fixed at 0.05.

Results

A total 84 pregnant women at term were initially eligible based on the established inclusion criteria. However, 32 (38.1 %) were later excluded: 7 patients were in early labour; 5 had multiple pregnancies; 4 had diabetes; 3 presented technical difficulties during PI measurement in the uterine/umbilical arteries; 2 had suspected preeclampsia; 8 were lost during follow-up; and 3 were excluded because of puerperium complications (2 had prolonged postpartum haemorrhage and 1 had surgical site infection).

Among the 52 enrolled women, 28 (53.8 %) were normotensive (NT), and 24 (46.2 %) had stage-1 chronic arterial hypertension (HT) (Table 1). The patient ages ranged from 17 to 42 years, and 67 % were less than 35 years. This was the first pregnancy in 65 % of the women. All delivered at term with a mean gestational age at delivery of 39.5 weeks [standard deviation (SD) 0.85]. There were significant differences between the NT and HT groups in parity (nulliparous predominated the HT group) and BMI (higher classes predominated the HT group).

During the puerperium, the presence of uterine artery notching increased over time from 6 to 98 % (Table 2) in both groups ($p < 0.001$). During the first (week 0) and third (week 4) time points, there were no significant differences between the NT and HT groups in the presence of notching; however, in the HT group, the majority of women exhibited positive notching at the second (week 1) time point [92 % (HT) vs 57 % (NT)], and the difference was statistically significant ($p = 0.013$). The mean (SD) of the MAP, BMI, and UtA-PIs at each time point and in each group are shown in Table 3. The crude effect of time on the mean MAP, BMI, and UtA-PIs is shown in Fig. 2. There was an overall decreasing trend in the mean MAP and BMI, and an increasing trend in the mean UtA-PI over time (Fig. 2a, b, and c, respectively).

The reliability coefficients were 0.080 and 0.457 for the transabdominal and transvaginal UtA-PI measurements, respectively. The intraclass correlation coefficient for the intra-observer reliability was 0.976 for the transabdominal (95 % CI 0.933–0.989) and 0.858 for the transvaginal (95 % CI 0.642–0.944) assessments, which is quite high [25].

Multivariate analysis

The net effect of time on the MAP, BMI, and UtA-PI was considered merely indicative; therefore, multivariate analyses were performed by adjusting the effect to potential

Table 1 Demographic characteristics of the study population

	All ($n = 52$)	Normotensive ($n = 28$)	Hypertensive ($n = 24$)	p value[b]
Age (intervals in years)				
17–24	8 (15 %)	3 (11 %)	5 (21 %)	0.359
25–34	27 (52 %)	17 (61 %)	10 (42 %)	
35–42	17 (33 %)	8 (28 %)	9 (37 %)	
Education level (years)				
<7	4 (8 %)	1 (4 %)	3 (12 %)	0.386
7–9	10 (19 %)	4 (14 %)	6 (25 %)	
10–12	23 (44 %)	13 (46 %)	10 (42 %)	
>12	15 (29 %)	10 (36 %)	5 (21 %)	
Smoking				
No	46 (88 %)	25 (89 %)	21 (87 %)	1.000
Yes	6 (12 %)	3 (11 %)	3 (13 %)	
Parity				
0	34 (65 %)	14 (50 %)	20 (83 %)	0.026
≥1	18 (35 %)	14 (50 %)	4 (17 %)	
Body mass index[a] (kg/m^2)				
18–24	19 (37 %)[c]	14 (50 %)	5 (21 %)	0.009
25–29	14 (27 %)[c]	9 (32 %)	5 (21 %)	
30–51	19 (37 %)[c]	5 (18 %)	14 (58 %)	
GA at delivery (weeks ± SD)	39.5 (0.85)	39.5 (0.87)	39.5 (0.85)	0.840
Birth weight at delivery (g), mean (SD)	3,239.4 (405.36)	3,209.5 (432.71)	3,274.4 (377.08)	0.566

BMI body mass index, *GA* gestational age, *SD* standard deviation

[a] BMI: measurement at time 0

[b] Tests homogeneity of proportions between the hypertensive and normotensive populations

[c] The summed relative frequencies in the three categories was 101 % due to rounding

Table 2 Absolute (relative, %) frequencies for positive notching of uterine arteries in normotensive and hypertensive women

Time (weeks)	All ($n = 52$)	p value[a]	Normotensive ($n = 28$)	Hypertensive ($n = 24$)	p value[b]
0	3 (6 %)	<0.001	1 (4 %)	2 (8 %)	0.590
1	38 (73 %)	<0.001	16 (57 %)	22 (92 %)	0.013
4	51 (98 %)	<0.001	27 (96 %)	24 (100 %)	1.000

[a] Tests the equality of population frequencies amongst positive and negative notching

[b] Tests the homogeneity of proportions between the hypertensive and normotensive populations

Table 3 Mean (standard deviation) MAP, BMI, and PI at each time point in the whole sample and stratified by hypertensive status

Weeks	Time points		
	0	1	4
All ($n = 52$)			
MAP	95.692 (13.189)	94.474 (12.486)	90.526 (9.911)
BMI	31.403 (5.488)	30.331 (5.449)	28.788 (5.522)
UtA-PI	0.808 (0.208)	1.301 (0.338)	1.915 (0.383)
Normotensive ($n = 28$)			
MAP	87.048 (9.070)	84.738 (6.868)	84.917 (7.446)
BMI	30.115 (5.759)	29.322 (5.805)	27.263 (5.630)
UtA-PI	0.746 (0.227)	1.134 (0.292)	1.832 (0.438)
Hypertensive ($n = 24$)			
MAP	105.778 (9.594)	105.833 (6.348)	97.069 (8.352)
BMI	32.907 (4.843)	31.507 (4.859)	30.568 (4.927)
UtA-PI	0.879 (0.159)	1.495 (0.283)	2.013 (0.286)

MAP mean arterial pressure, *BMI* body mass index, *UtA-PI* uterine artery pulsatility index

confounders and accommodating the study design. Known confounding variables such as maternal age, BMI, and parity were also considered in the analysis; they were not statistically significant and were not considered in the final model.

MAP and BMI models

Although the mean MAP significantly decreased over time ($p < 0.05$) in the HT group, the time variable failed to have a significant effect in the NT group (Fig. 3a). The corresponding model is described in the "Statistical analysis" section; estimates of the coefficients and respective 95 % confidence intervals are presented in Table 4. The predicted BMI and the 95 % confidence intervals for the NT and HT group over time are shown in Fig. 3b. In both groups, the BMI exhibited a decreasing trend, but there was no significant difference between the NT and HT groups. Estimates of the coefficients and 95 % confidence

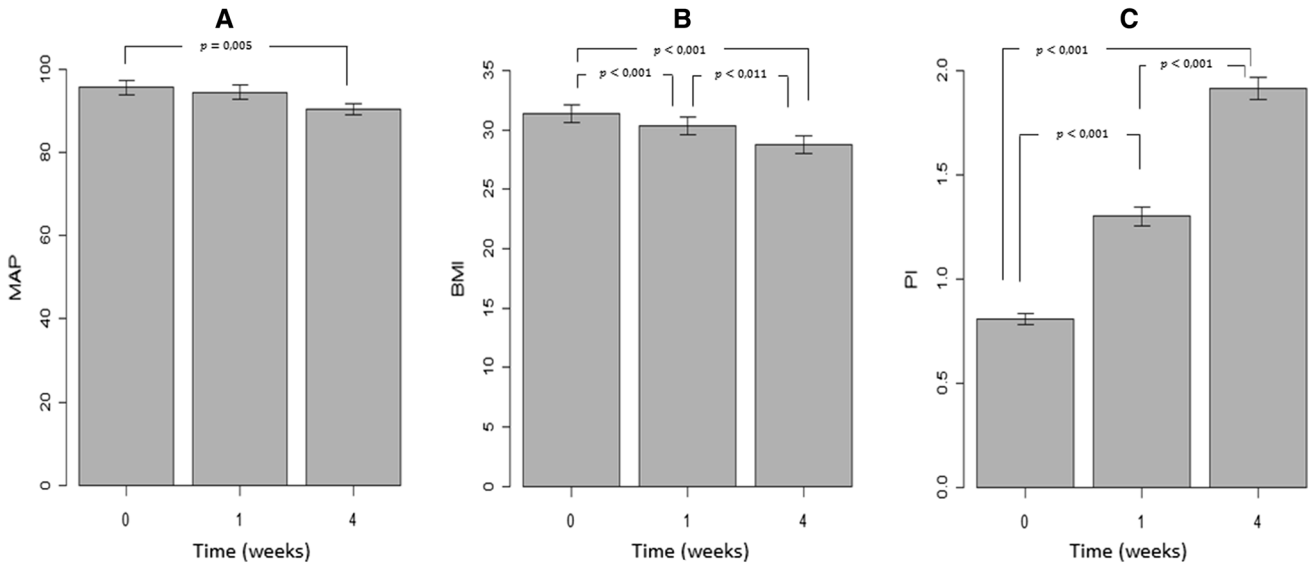

Fig. 2 Mean (±standard deviation) MAP (**a**), BMI (**b**), and UtA-PI (**c**) at each time point in the entire sample. *MAP* mean arterial pressure, *BMI* body mass index, *UtA-PI* uterine artery pulsatility index

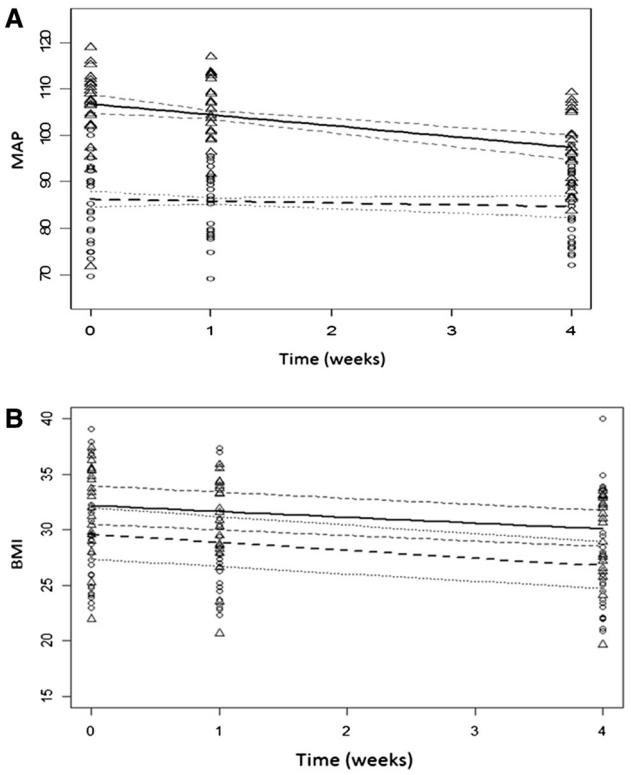

Fig. 3 Predicted mean arterial pressure (**a**) and body mass index (**b**) over time in normotensive (*dashed line*, *circles*) and hypertensive (*solid line*, *triangles*) women. The 95 % confidence intervals for the respective predictions are indicated (*dashed bands*)

Table 4 Estimated coefficients and correlation of the regression model predicting the MAP at different covariates combinations

Covariates	Coefficient	95 % CI
Intercept	86.338*	84.533, 87.922
Hypertension	20.581*	17.989, 23.173
Time	−0.396	−1.413, 0.621
Hypertension × time	−1.953*	−3.449, −0.456

MAP mean arterial pressure, *CI* confidence interval

* $p < 0.05$

intervals for the corresponding model are presented in Table 5.

UtA pulsatility indices

The predicted and observed mean UtA-PI in the NT and HT groups are depicted in Fig. 4. In both groups, the uterine artery impedance showed a significant increase over time ($p < 0.05$). Additionally, the PI in the HT group was significantly higher over time compared with the NT group. The estimated coefficients of the regression model used to predict the PI at the different covariates combinations are presented in Table 6.

Table 5 Estimated coefficients, correlation, and variance parameters of the regression model predicting the BMI at different covariates combinations

Covariates	Coefficient	95 % CI
Intercept	3.387*	3.309, 3.465
Hypertension	0.084	−0.011, 0.179
Time	−0.025*	−0.031, −0.020
Hypertension × time	0.008*	0.001, 0.015
Correlation parameter	0.955	
Variance factor for hypertension	0.640	

BMI body mass index, *CI* confidence interval

* $p < 0.05$

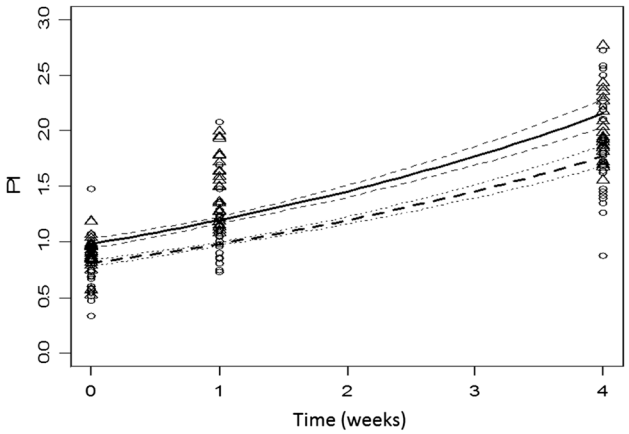

Fig. 4 Predicted mean pulsatility (PI) index of the uterine artery over time in normotensive (*dashed line*, *circles*) and hypertensive (*solid line*, *triangles*) women. The 95 % confidence intervals for the respective predictions are indicated (*dashed bands*)

Table 6 Estimated coefficients, correlation, and variance parameters of the regression model predicting the uterine artery PI at different covariates combinations

Covariates	Coefficient	95 % CI
Intercept	−0.215*	−0.254, −0.293
Hypertension	0.197*	0.177, 0.217
Time	0.197*	0.173, 0.220
Correlation parameter	−0.012	
Variance factor for hypertension	0.821	

PI pulsatility index, *CI* confidence interval

* $p < 0.05$

Discussion

During pregnancy, remarkable circulatory changes occur in the pelvis because the foetus has increased nutritional demands that the uterine circulation must accommodate. As expected, the uterine artery, as the immediate

intervenient in this process, has become an important target in obstetrical Doppler ultrasound studies. Several reports performed at different gestational ages have shown that the uterine artery impedance provides relevant predictive information on serious maternal and foetal complications. As a result, UtA-PI and notch assessment has been recommended for use in daily clinical practice [16]. Although the value of UtA impedance assessment during pregnancy is unquestionable, its postpartum utility is less clear and has received less attention. Yet, the ability to predict certain postpartum pathologies would be immensely useful; therefore, appropriate prognostic tools are needed. Among the potential complications, PE, postpartum haemorrhage, retained placental tissue, and infection are particularly relevant.

After delivery, remarkable structural and functional changes occur in the uterus to re-establish the non-pregnant condition, starting immediately upon placenta delivery and continuing for the following 6–8 weeks. This transition involves the spiral arteries, whose high capacitance properties are no longer necessary; as a result, the lumen is obliterated through thrombosis, endarteritis, and intima thickening [26]. Despite the substantial vascularization that is still present [18], the occlusion increases the local vascular resistance [27, 28]. The immediate cause for these events is the pressure imposed by the brisk postpartum myometrium contraction, but there is evidence that it may also be mediated immunologically because defects in complement expression have been observed in cases of placental site subinvolution [29].

In our investigation, the uterine artery PI was assessed during the recognised period of uterine involution; based on the study design, we are convinced that the changes reflected are quite specific and intrinsic patterns of postpartum involution as variables associated with labour differences were precluded. In this study, we examined the uterine arterial circulation after caesarean section in the absence of labour, which ensured the absence of any confounding effect related to other modes of delivery (spontaneous vaginal, ventouse, or forceps) and labour-related variables such as dystocia, phase latency variability, first stage duration, and myometrial contraction.

In normotensive women, the UtA-PI was significantly increased during the puerperal period. Interestingly, the mean value at the first time point, i.e., immediately before the caesarean section, is quite similar to the previously reported third trimester mean [30]. Although there may be some variability in the specific postpartum period assessed, the observed increase in the vascular resistance is consistent with most studies [17–19]. Few studies report no change [31], likely reflecting design variation.

An important novel finding in the current study concerns the UtA-PI in women with chronic hypertension and uncomplicated pregnancies. Again, the mean PI at the first time point was similar to the previously reported third trimester value in hypertensive women [30], and at the remaining time points, the UtA-PI progressively increased postpartum at a rate similar to that in normotensive women. However, the UtA-PI increases at higher magnitude compared with that in normotensive women. Remarkably, this peri- and postpartum difference has been recognised at other points during pregnancy [30]. Although the cause of this UtA-PI increase in normotensive and hypertensive women is unknown, the decreased concentration of locally active compounds such as oestradiol or progesterone, which decrease substantially after delivery [32], cannot be ignored.

Less clear is the cause of the parallel UtA-PI increase observed in both groups. We suspect that this trend, which was stable and continuous despite the dramatic uterine changes, reflects the steady and robust regulatory mechanisms in the vasculature. The responsible mechanisms may be systemic as those thought to control essential hypertension [33], but they may also reflect local activity, pregnancy-dependent factors, or genetic modulations that collectively allow the UtA to adequately perfuse the uterus irrespective of its pathologic condition. For example, women of Andean ancestry exhibit a three times higher UtA-PI compared with women of European descent, despite living at similar altitudes; however, during pregnancy, the hemodynamic adjustments lead to rather similar UtA-PIs in both [34].

An understanding of the uterine impedance recovery during the puerperium returning to the non-pregnant condition can help show the normal physiology and provide important insights into specific disorders, with PE as the most important one. The morbidity and mortality associated with PE cannot be overlooked, and delivery does not completely eliminate the risk of PE and its complications, which can become apparent when successful treatment has been seemingly achieved [20, 35]. Indeed, PE frequently shows up without any clinical signs or may present with non-specific or mild symptoms [36].

A number of molecules with local and systemic action have been shown to modulate the occurrence of PE including nitric oxide, components of the renin–angiotensin system, and certain growth factors [37], but assessment is cumbersome or clinically unfeasible. During the puerperal period, apart from continued monitoring and reporting of signs and symptoms, a hemodynamic approach, such as uterine artery impedance measurement, could be a useful way to detect impending PE or other conditions. However, additional studies are required to verify the diagnostic or prognostic utility of UtA Doppler ultrasound for specific hypertensive syndromes puerperium.

Study limitations

The present study comprised only uneventful pregnancies with normal neonatal and puerperal outcomes, and cannot be extrapolated to patients with other hypertensive conditions during pregnancy. Additionally, the hypertensive patients were treated from the first trimester onwards with daily low-dose acetylsalicylic acid and methyldopa. However, this regimen was prescribed in all the hypertensive patients, and therefore, this confounder was not isolated in the statistical analysis (the proportions were 100 and 0 %, respectively).

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Conflict of interest The authors declare that they have no conflict of interest.

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