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Peripheral maternal haemodynamics across pregnancy in hypertensive disorders of pregnancy

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\textbf{ABSTRACT}

\textbf{Objectives:} Evaluating maternal haemodynamics across pregnancy in uncomplicated pregnancies and those complicated by hypertensive disorders of pregnancy (HDP).

\textbf{Study design:} Prospective cohort study from 2015 to 2018 of healthy, nulliparous, singleton-bearing women. Maternal haemodynamics assessed by Uscom BP+ at 9–16 and 32–36 weeks’ gestation in pregnancies complicated by HDP (preeclampsia with severe (sPE n = 12) and without severe clinical features (nsPE n = 49), gestational hypertension (GH n = 25), transient gestational hypertension (TGH n = 33)) were compared to uncomplicated pregnancies (n = 286) using mixed-effects linear modelling.

\textbf{Main outcome measures:} Maternal haemodynamic adaptation in uncomplicated pregnancies and those complicated by HDP.

\textbf{Results:} Between the two measurements, haemodynamic adaptation in women with sPE and nsPE was significantly different compared to those with uncomplicated pregnancies. An additional increase was observed for peripheral systolic blood pressure [SBP; 14.3 mmHg, 8.6–20.1 (sPE)], peripheral diastolic blood pressure [DBP; 7.7 mmHg, 3.3–12.1 (sPE); 2.6 mmHg, 3.3–12.1 (nsPE)] peripheral mean arterial pressure [MAP; 10.6 mmHg, 5.8–15.5 (sPE); 3.4 mmHg, 0.8–6.0 (nsPE)], peripheral pulse pressure [PP; 2.9 mmHg, 0.1–5.8 (nsPE)], central SBP [15.8 mmHg, 10.4–21.2 (sPE); 2.9 mmHg, 0.1–5.8 (nsPE)], central DBP [8.3 mmHg, 3.9–12.6 (sPE); 2.5 mmHg, 0.2–4.8 (nsPE)], central MAP [10.8 mmHg, 6.4–15.2 (sPE); 2.6 mmHg, 0.3–5.0 (nsPE)] and central PP [7.6 mmHg, 3.9–11.3 (sPE)]. Augmentation index (AIx) decreased less (15.5%, 6.3–24.6 (sPE); 9.0%, 4.2–13.6 (nsPE)] compared to uncomplicated pregnancies. Haemodynamic adaptation across pregnancy in women with GH and TGH was not different from those with uncomplicated pregnancies.

\textbf{Conclusion:} Women who develop preeclampsia show an altered, while those who develop GH or TGH demonstrate a comparable haemodynamic adaptation compared to uncomplicated pregnancies. TGH is not a benign condition.

\textbf{Abbreviations:} AIx, augmentation index; BMI, body mass index; BP, blood pressure; cBP, central blood pressure; cDBP, central diastolic blood pressure; CI, confidence interval; cMAP, central mean arterial pressure; cPP, central pulse pressure; CS, caesarean section; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; HR, heart rate; ISSHP, International Society for the Study of Hypertension in Pregnancy; MAP, mean arterial pressure; nsPE, preeclampsia without severe clinical features; pBP, peripheral blood pressure; pDBP, peripheral diastolic blood pressure; pMA, peripheral mean arterial pressure; PE, preeclampsia; PWV, pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; SES, socioeconomic status; SGA, small-for-gestational-age; sPE, preeclampsia with severe clinical features; SNR, signal-to-noise ratio; STOP, Screening Tests to predict poor Outcomes of Pregnancy; TGH, Transient gestational hypertension

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1. Introduction

During pregnancy, substantial maternal haemodynamic changes take place to ensure adequate placental perfusion, as well as nutrient and gaseous transport, to sustain fetal growth and development [1]. Early maternal haemodynamic maladaptation to pregnancy can signal an increased risk for preeclampsia (PE) [1].

In recent years, sophisticated non-invasive equipment has become available to assess the maternal haemodynamic state, allowing safe monitoring of haemodynamic changes throughout pregnancy [2]. Altered haemodynamics have been identified in women who develop pregnancy complications, particularly in those who develop PE [2–8]. Increased pulse wave velocity (PWV) and augmentation index (AIx), measures of arterial stiffness, have been reported as early as 11 weeks’ gestation in women who subsequently develop PE [5–8]. Also, these women demonstrate an increase in central systolic blood pressure (cSBP), PWV and AIx at time of PE diagnosis [2–4].

The aim of this study was to compare maternal haemodynamic adaptation at 9–16 and 32–36 weeks’ gestation in uncomplicated pregnancies and those complicated by HDP.

2. Methods

The Screening Tests to predict poor Outcomes of Pregnancy (STOP) study is a prospective multicentre cohort study of healthy, nulliparous, singleton-bearing women across three Hospitals in Adelaide, South Australia (Lyell McEwin Hospital, Elizabeth Vale; Modbury Hospital, Modbury and Women’s and Children’s Hospital, North Adelaide) from 2015 to 2018. Women were excluded from participation if they had ≥3 miscarriages or ≥3 terminations of pregnancy, major fetal anomalies, pre-existing hypertension on medication, Type I or Type II diabetes mellitus, renal disease, systemic lupus erythematosus, anti-phospholipid syndrome, known major uterine anomaly or previous cervical cone biopsy.

At time of recruitment, between 9 and 16 weeks’ gestation, participants were interviewed. Comprehensive baseline information regarding demographics, family medical and obstetric history, dietary supplementation and nutrition was collected. In addition, anthropometric measurements and maternal haemodynamic measurements (explained below) were performed. All women participating in the STOP study were invited to attend a follow-up between 32 and 36 weeks’ gestation. During this follow-up, participants had an interview regarding current pregnancy issues, medication use, dietary supplements and nutrition. Anthropometric and maternal haemodynamic measurements were repeated.

At both study visits, brachial oscillometric pulse wave analysis (Uscom BP+) was used to ascertain maternal haemodynamic state. Uscom BP+ is a validated method to measure peripheral blood pressures [BP; peripheral systolic BP (pSBP); peripheral diastolic BP (pDBP)]; peripheral mean arterial pressure (pMAP); peripheral pulse pressure (pPP); central BP [central systolic BP (cSBP); central diastolic BP (cDBP)]; central mean arterial pressure (cMAP); central pulse pressure (cPP)] and measure AIx and heart rate (HR) [9,10]. Uscom BP+ is a fully-automated device with a pneumonic cuff. During an initial inflation and deflation period it measures pBP. Then, it reinflates approximately 30 mmHg above the pSBP, occluding the brachial artery for 10 s, while the device records the suprasystolic BP waves and determines cBP [11–13]. Peripheral AIx is estimated using the following equation [9]:

\[
\text{Peripheral AIx} = \frac{\text{late systolic pressure (P2)}}{\text{early systolic pressure (P1)}}
\]

All measurements were performed under standardized conditions, in a semi-recumbent position, using an appropriate cuff size and following a 5-minutes period of physical inactivity. The quality of the measurements was ensured by an in-built quality control feature, expressed as a signal-to-noise ratio (SNR) on a logarithmic scale in decibels. Signal quality score was classified into 5 groups: invalid (SNR < 0), poor (0 ≤ SNR < 6), acceptable (6 ≤ SNR < 9), good (9 ≤ SNR < 12) and excellent (12 ≤ SNR) [14]. Measurements with an invalid or poor quality score were repeated, until an at least acceptable score was obtained.

Fetal and maternal outcomes were obtained directly from clinical records. The diagnosis of HDP was made according to the criteria of the International Society for the Study in Hypertension in Pregnancy (ISSHP) [15,16]. Gestational hypertension (GH) was defined as (peripheral) hypertension [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] after 20 weeks of gestation in previously normotensive women. PE was defined as GH associated with one or more of the following new-onset conditions: 1. Proteinuria (protein/creatinine ≥ 30 mg/mmol [0.3 mg/mg] or ≥ 300 mg/day; 2. Other maternal dysfunction (renal insufficiency, liver involvement, neurological complications or haematological complications); 3. Uteroplacental dysfunction (small-for-gestational-age infant with a birth weight less than the 10th customised centile) [15]. PE with severe clinical features (sPE) was defined as PE with one or more of the following clinical features: BPs of ≥ 160/110 or hypertension requiring intravenous therapy with an antihypertensive agent or magnesium sulphate after 20 weeks of gestation, HELLP syndrome or eclampsia at any gestation. PE without any of these severe clinical features was classified as PE without severe clinical features (nPE). Transient Gestational Hypertension (TGH) was defined as non-persisting hypertension on one or two occasions, not formally meeting the definitions of GH. Uncomplicated pregnancies were defined as uneventful pregnancies with normal fetal and maternal outcomes, specifically, the absence of any of the above mentioned complications, and additionally, the absence of preterm birth before 37 weeks, small-for-gestational-age < 10th customised birth weight centile, gestational diabetes mellitus, placental abruption and cholestasis.

Statistical analyses were performed with SPSS version 24.0 (SPSS Inc. 2016). One-way ANOVA analyses were used for comparisons between continuous variables and Chi-square for categorical variables. Differences were considered significant when the p-value was less than 0.05. Simple linear modelling was used to compare means of the haemodynamic parameters at the two individual time points between the HDP groups. Descriptive means and standard deviations (SDs) were reported along with the Bonferroni adjusted post-hoc p-values. To assess change in haemodynamic parameters across gestation analyses of repeated measures with mixed-effects linear models (fixed effects and random effects) were performed. Residuals of each individual model were assessed for normality, allowing interpretation of the models. The random effect component consisted of a random intercept for each patient. The fixed-effect component included HDP groups, timing of measurement (first measurement at ~ 11 or second measurement at ~34 weeks’ gestation), baseline measurement at 11 weeks’, maternal age and body mass index (BMI) and interaction between timing of measurement and the different HDP groups. The latter was used to assess the change over time. The mean estimated difference and 95%-confidence intervals (CIs) of the interaction term are also reported to describe the additional change in the mean differences between HDP groups across the two measurements.

Written informed consent was obtained from all participants. Personal identifying information in the STOP study database was eliminated to ensure that confidentiality of all patients’ records was maintained. The STOP study protocol was approved by the Human Research Committee of the Women’s and Children’s Hospital Adelaide Australia (HREC/14/WCHN/90), dated 16/10/2014.

3. Results

Both study visits were attended by 551 participants and pregnancy outcome variables were available for 544 (98.7%) women. Twelve women (2.2%) had sPE, 49 (9.0%) had nPE, 25 (4.6%) had GH, 33
(6.1%) had TGH and 286 (52.8%) an uncomplicated pregnancy. A total of 405 women were assessed, because a further 138 (25.4%) women were diagnosed with other complications of pregnancy, including preterm birth, (normotensive) small-for-gestational age, gestational diabetes mellitus and cholestasis, and therefore not included in the analysis. The mean gestational age for the study group (33.6%). There were no significant differences in incidence of GDM, preterm birth and SGA between the HDP groups (by ISSHP definition GH pregnancies do not result in SGA neonates).

### 3.1. Maternal haemodynamics at 11 and 34 weeks’ gestation

In the 5 HDP groups combined, there were a total of 810 paired measurements performed in 405 women.

At 11 weeks’ gestation, women with uncomplicated pregnancies showed mean pSBP 113.3 mmHg, pDBP 66.9 mmHg, pPP 46.4 mmHg, pMAP 79.8 mmHg, cSBP 104.3 mmHg, cDBP 69.9 mmHg, cPP 34.4 mmHg, cMAP 81.4 mmHg, Afx 48.0% and HR 78.1 bpm (Table 2, Figs. 1 and 2). At 11 weeks’, women who subsequently developed any HDP subtype showed an increased mean pDBP, pMAP and cDBP compared to those with uncomplicated pregnancies. Additionally, pPP was increased in those who subsequently developed sPE and GH, but not in those who later developed TGH and sPE. Compared to uncomplicated pregnancies, cPP, Afx and HR were not different in women.
who developed HDP.

At 34 weeks' gestation, women with uncomplicated pregnancies showed mean pSBP 116.1 mmHg, pDBP 68.9 mmHg, pPP 45.6 ± 5.1, cSBP 104.3 ± 9.5, cDBP 74.8 ± 7.5, cPP 34.4 ± 7.0, cMAP 81.4 ± 7.4, AIX 48.0 ± 17.7, HR 78.1 ± 11.1 compared to those who developed HDP, compared to women with uncomplicated pregnancies. The change across gestation, after adjustment, for pSBP, pDBP, pMAP, pPP, cSBP, cDBP, cMAP, cPP and AIx was different from those with uncomplicated pregnancies. AIX was increased in women who developed sPE and nsPE, while the GH and TGH women demonstrated a similar AIX decrease to uncomplicated pregnancies (Fig. 4). The increase in HR across gestation in each HDP group was similar to uncomplicated pregnancies.

4. Discussion

This study observed differences in haemodynamic parameters at 9–16 and 32–36 weeks' gestation and across gestation in women who developed HDP, compared to women with uncomplicated pregnancies.

4.1. Maternal haemodynamics in pregnancies complicated by HDP

Compared to women with uncomplicated pregnancies, those who developed sPE had increased pSBP, pDBP, cDBP and cMAP at 11 weeks', while pSBP, pDBP, pPP, cSBP, cDBP, cMAP, cPP and AIX were increased at 34 weeks'. They showed increased adjusted mean difference across gestation for pSBP, pDBP, pMap, pPP, cSBP, cDBP, cMAP, cPP and AIX were increased at 34 weeks'. Across gestation they had an increased adjusted mean difference for pSBP, pDBP, pPP, cSBP, cDBP, cMAP and AIX, compared to women with uncomplicated pregnancies. In addition to having a higher blood pressure at 11 weeks, these data demonstrate that women who developed sPE and nsPE failed to haemodynamically adapt to pregnancy.

Women who subsequently developed GH, showed increased haemodynamic parameters at 11 and 34 weeks' gestation, compared to those with uncomplicated pregnancies. At 11 weeks' these women had increased pSBP, pDBP, pMAP, pPP, cSBP, cDBP and cMAP. These parameters, as well as cPP, were also increased at 34 weeks'. The corrected mean difference across gestation was however comparable to those with uncomplicated pregnancies. Women who developed GH have increased haemodynamic parameters throughout pregnancy while the haemodynamic adaptation, specifically AIX, is quite similar to uncomplicated pregnancies.

Women with TGH showed increased pSBP, pDBP, pMAP, cSBP, cDBP and cMAP at 11 and 34 weeks' gestation, but the mean adjusted difference across gestation was comparable to those with
Fig. 1. Means of peripheral and central measurements at 11 and 34 weeks of gestation for different HDP groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, PP, pulse pressure.

Fig. 2. Means for augmentation index (A) and heart rate (B) at 12 and 34 weeks' gestation for different HDP groups.
uncomplicated pregnancies. This suggests that women who develop TGH have increased haemodynamic parameters throughout pregnancy. Also, like GH, maternal haemodynamic adaptation to pregnancy is of similar magnitude as for women with uncomplicated pregnancies. The elevated haemodynamic parameters and increased risk of SGA in women with TGH suggests that TGH is not a benign condition, a risk often not recognized by clinicians, despite being recognised by other studies and the ISSHP [15–17].

4.2. Central blood pressure and augmentation index

It is suggested that cBP reflects accurately the loading conditions of the left ventricular myocardium, coronary arteries, and cerebral vasculature [2]. Theoretically, it is a better reflection of potential risk of cardiovascular organ damage and cardiovascular events than pBP [2]. Non-invasively determined cPP is more strongly related to vascular and ventricular hypertrophy, extent of atherosclerosis, and cardiovascular events than pBP [2]. In the present study, cPP was increased at 34 weeks’ in women who developed sPE and GH. The SDs during both measurements were less for cBP, than pBP, indicating a lesser variation in cBP than pBP. Now cBP can be measured non-invasively, reliably [10], and cost-effectively [18], in addition to the previous mentioned benefits, it should be considered in the clinic for the monitoring of women at risk of HDP. Additional research should test the utility of adding central blood pressure measurements for risk prediction of pregnancy complications.

Fig. 3. Differences in estimated marginal means in blood pressure across gestation in each hypertensive disorder of pregnancy (HDP) group. Data are presented as corrected mean difference (mmHg) across gestation compared to uncomplicated pregnancies. Values with an asterix indicate significant mean differences compared to women with uncomplicated pregnancies. Mean differences in the model were corrected for mean maternal age (26.1 years), mean maternal BMI (28.2 kg/m²) and their mean baseline measurement (pSBP: 116.2 mmHg; pDBP: 68.8 mmHg; pMAP: 81.9 mmHg; pPP: 47.7 mmHg; cSBP: 105.9 mmHg; cDBP: 71.4 mmHg; cMAP: 82.9 mmHg; cPP: 34.6 mmHg).
Aix is considered to be a measure of arterial stiffness, influenced by wave reflections from the arterial vessel tree [19,20]. It is likely that Aix depends on the diameter and elasticity of the small muscular arteries/arterioles at the major sites of pressure wave reflection. Therefore, it will be affected by alterations in vascular smooth muscle tone, affecting mainly the small muscular arteries but to a lesser extent in the elastic aorta [19]. An increased Aix is considered to be an indicator of increased work by the left ventricle during systole and may be a more direct measure of vascular tone or vasoconstriction than PWV [19]. Arterial stiffness better reflects chronic damage to blood vessels form aging, hypertension and diabetes than pBP or even cBP. In our study, Aix decreased less in women who developed sPE and nsPE, while women with GH and TGH demonstrated a similar Aix decrease to those with uncomplicated pregnancies. This agrees with data from other studies and indicates that women with PE fail to haemodynamically adapt to pregnancy [21–23].

4.3. Strengths and limitations

A strength of this study is its prospective character and extensive amount of data collected. The study was large enough to identify differences in maternal haemodynamics across gestation in women with HDP compared to those with uncomplicated pregnancies, but larger numbers of women are necessary to identify if there are differences between HDP groups. Due to the design of this study, we were unable to assess maternal haemodynamics across gestation in women who suffered from early-onset PE, resulting in delivery before 32 weeks. Uscom BP+ provides a comprehensive assessment of the haemodynamic state, including cBP and Aix, but does not assess PWV.

The nulliparous pregnancies reported in this study showed higher incidences for gestational hypertension and preeclampsia than published national Australian incidences. The hospital in which this study was conducted serves a low-socioeconomic status (SES) community with high rates of unemployment, unstable relationships, drug use, poor diet and obesity [24]. The incidence of gestational hypertension and preeclampsia in this study cohort with paired measurements do not reflect the Australian or South-Australian population. It may be more important to assess haemodynamic status in early pregnancy in low SES women.

5. Conclusion

This study demonstrates that GH and PE have a different vascular pathophysiology and are two different disease entities. Women who developed sPE and nsPE fail to haemodynamically adapt to pregnancy, while already starting from a higher blood pressure at baseline. Women who developed GH had increased haemodynamic parameters in first and third trimester, but their haemodynamic adaptation to pregnancy was comparable to those with uncomplicated pregnancies. Despite haemodynamic adaptation to pregnancy comparable to uncomplicated pregnancies, women who developed TGH had elevated haemodynamic parameters in first and third trimester and higher risk of SGA, indicating that TGH is not a benign condition and deserves attention in antenatal care. Measurements of cBP and Aix give additional information on haemodynamic state and should be considered in the clinic for the monitoring of women at risk of HDP.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.02.006.

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