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CHAPTER 5

PERIPHERAL MATERNAL HAEMODYNAMICS ACROSS PREGNANCY IN HYPERTENSIVE DISORDERS OF PREGNANCY.

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ABSTRACT

OBJECTIVES

Evaluating maternal haemodynamics across pregnancy in uncomplicated pregnancies and those complicated by hypertensive disorders of pregnancy (HDP).

STUDY DESIGN

Prospective cohort study from 2015-2018 of healthy, nulliparous, singleton-bearing women. Maternal haemodynamics assessed by Uscom BP+ at 11^{+2} and 34^{+2} weeks' gestation in pregnancies complicated by HDP [preeclampsia with severe (sPE) and without severe features (nsPE), gestational hypertension (GH), intermittent hypertension (IH)] were compared to uncomplicated pregnancies using mixed-effects linear modelling.

MAIN OUTCOME MEASURES

Maternal haemodynamic adaptation in women with uncomplicated pregnancies and those complicated by HDP.

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; 14.3mmHg, 8.6-20.1 (sPE)], peripheral diastolic blood pressure [DBP; 7.7mmHg, 3.3-12.1 (sPE); 2.6mmHg, 3.3-12.1 (nsPE)] peripheral mean arterial pressure [MAP; 10.6mmHg, 5.8-15.5 (sPE); 3.4mmHg, 0.8-6.0 (nsPE)], peripheral pulse pressure [PP; 6.6mmHg, 2.1-11.1 (sPE)], central SBP [15.8mmHg, 10.4-21.2 (sPE)]; 2.9mmHg, 0.1-5.8 (nsPE)], central DBP [8.3mmHg, 3.9-12.6 (sPE); 2.5mmHg, 0.2-4.8 (nsPE), central MAP [10.8mmHg, 6.4-15.2 (sPE); 2.6mmHg, 0.3-5.0 (nsPE)] and central PP [7.6mmHg, 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 IH was not different from those with uncomplicated pregnancies.

CONCLUSION

Women who develop preeclampsia show an altered, while those who develop GH or IH demonstrate a comparable haemodynamic adaptation compared to uncomplicated pregnancies. Monitoring central blood pressure and AIx in pregnancy provides additional value.

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[3,4,2,5–8]. 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[5–7,9]. Also, these women demonstrate an increase in central systolic blood pressure (cSBP), PWV and AIx at time of PE diagnosis[3,4,2].

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.

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 2015-2018. 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^{+0} and 16^{+0} 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 31^{+5} and 37^{+2} 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)[10,11]. 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 30mmHg above the pSBP, occluding the brachial artery for 10 seconds, while the device records the suprasystolic BP waves and determines cBP[12–14]. Peripheral AIx is estimated using the following equation[10]:

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

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)[15]. Measurements with an invalid or poor quality score were repeated, until an at least acceptable score was obtained. Where no acceptable measurement could be obtained, data were excluded from the analyses.

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)[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)[16]. PE with severe features (sPE) was defined as PE with one or more of the following features: BP 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 features was classified as non-severe PE (nsPE). In addition to the ISSHP classification 'intermittent hypertensive' (IH) 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.

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 nsPE, 25 (4.6%) had GH, 33 (6.1%) had IH and 286 (52.8%) an uncomplicated pregnancy. A further 138 (25.4%) women were diagnosed with other complications of pregnancy. The mean gestational age for the first measurement was 11^{+2} ($\pm 1^{+3}$) weeks' and for the second measurement it was 34^{+2} ($\pm 1^{+4}$) weeks'. There were no differences between the groups regarding the gestational age at which these measurements were performed (p=0.603 and p=0.102 respectively).

The 5 groups were comparable in terms of maternal age, ethnicity, marital status, education, employment, (household) smoking, alcohol and drug use, mode of conception and fetal sex (Table 1). There were differences between the HDP groups regarding maternal BMI and family history for HDP and chronic hypertension. Women with GH were on average heaviest (mean BMI 32.4 ± 10.3), while women with uncomplicated pregnancies had on average the lowest BMI (mean BMI 27.2 ± 6.5). A family history of HDP was increasingly more common between HDP groups, with 11.5% in uncomplicated pregnancies versus 33.3% in women with sPE. A family history of chronic hypertension was more common in all HDP groups (varying from 41.7% to 51.5%) compared to the uncomplicated 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).

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Table 1. Maternal demographics, pregnancy and neonatal outcome

	Uncompli-cated	IH	GH	nsPE	sPE	
	(n=286)	(n=33)	(n=25)	(n=49)	(n=12)	
Demographics	n (%)	n (%)	n (%)	n (%)	n (%)	p
Maternal age						0.173
< 20 years	19 (6.6)	2 (6.1)	1 (4.0)	3 (6.1)	2 (16.7)	
20-25	87 (30.4)	10 (30.3)	8 (32.0)	17 (34.7)	4 (33.3)	
25-30	123 (43.0)	13 (39.4)	8 (32.0)	21 (42.9)	2 (16.7)	
30-35	45 (15.7)	8 (24.2)	6 (24.0)	5 (10.2)	1 (8.3)	
> 35 years	12 (4.2)	0 (0.0)	2 (8.0)	3 (6.1)	3 (25.0)	
BMI at booking						*0.009*
<18.5 - Underweight	3 (1.0)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	
18.5 -< 25.0 - Normal weight	122 (42.7)	10 (30.3)	5 (20.0)	11 (22.4)	3 (25.0)	
25.0 -< 30.0 - Overweight	88 (30.8)	5 (15.2)	9 (36.0)	14 (28.6)	3 (25.0)	
30.0 -< 40.0 - Obese	56 (19.6)	14 (42.4)	6 (24.0)	19 (38.8)	5 (41.7)	
>40.0 - Morbidly obese	17 (5.9)	3 (9.1)	5 (20.0)	5 (10.2)	1 (8.3)	
Ethnicity						0.840
Caucasian	246 (86.0)	30 (90.9)	23 (92.0)	45 (91.8)	12 (100.0)	
Asian	21 (7.3)	2 (6.1)	1 (4.0)	2 (4.1)	0 (0.0)	
Other	19 (6.6)	1 (3.0)	1 (4.0)	2 (4.1)	0 (0.0)	
Marital status						*0.010*
Stable relationship	259 (90.9)	28 (84.8)	21 (84.0)	43 (87.8)	7 (88.6)	
Single	24 (8.4)	5 (15.2)	4 (16.0)	6 (12.2)	4 (10.6)	
Same sex	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	
Substance use @ booking						
Smoking	43 (15.0)	4 (12.1)	6 (24.0)	6 (12.2)	3 (25.0)	0.565
Alcohol	41 (14.3)	6 (18.2)	7 (28.0)	10 (20.4)	4 (33.3)	0.180
Recreational drug use	6 (2.1)	0 (0.0)	1 (4.0)	2 (4.1)	0 (0.0)	0.702
Family history						
HDP	33 (11.5)	6 (18.2)	7 (28.0)	11 (22.4)	4 (33.3)	*0.021*
Chronic hypertension	96 (33.6)	17 (51.5)	12 (48.0)	25 (51.0)	5 (41.7)	*0.049*
Pregnancy characteristics						
Male fetal sex	154 (53.8)	17 (51.5)	17 (68.0)	32 (65.3)	6 (50.0)	0.385
Birthweight (g)*	3553 ±379	3411 ±531	3378 ±350	3204 ±539	2962 ±668	*<0.001*
Gestation at delivery (weeks)*	40.0 ±1.0	39.5 ±1.5	38.9 ±1.3	39.1 ±1.4	38.1 ±2.2	*<0.001*
Nursery admission	43 (15.0)	11 (33.3)	6 (24.0)	15 (30.6)	7 (58.3)	*0.000*
GDM	N/A	7 (21.2)	4 (16.0)	10 (20.4)	2 (16.7)	0.952
Preterm birth (<37 weeks)	N/A	2 (6.5)	2 (8.0)	4 (8.2)	5 (41.7)	0.555
SGA	N/A	8 (24.2)	N/A	15 (30.6)	3 (25.0)	0.799

IH, intermittent hypertensive; GH, gestational hypertension; nsPE, preeclampsia without severe features; sPE, preeclampsia with severe features; HDP, Hypertensive disorders of pregnancy; CS, Caesarean Section; GDM, Gestational diabetes mellitus; PTB, Preterm birth (<37 weeks); SGA, Small for gestational age.
* Expressed as mean ±SD

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Maternal haemodynamics at 11 and 34 weeks' gestation

In the 5 HDP groups combined, there were a total of 810 paired measurements were performed in 405 women. At 11 weeks' gestation, women with uncomplicated pregnancies showed mean pSBP 113.3mmHg, pDBP 66.9mmHg, pPP 46.4mmHg, pMAP 79.8mmHg, cSBP 104.3mmHg, cDBP 69.9mmHg, cPP 34.4mmHg, cMAP 81.4mmHg, AIx 48.0% and HR 78.1bpm (Table 2, Figures 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. Women who later developed nsPE, GH and IH, but not those who subsequently developed sPE, had also an increased mean pSBP, cSBP and cMAP at 11 weeks' compared to those with uncomplicated pregnancies. Additionally, pPP was increased in those who subsequently developed nsPE and GH, but not in those who later developed IH and sPE. Compared to uncomplicated pregnancies, cPP, AIx and HR were not different in women who developed HDP.
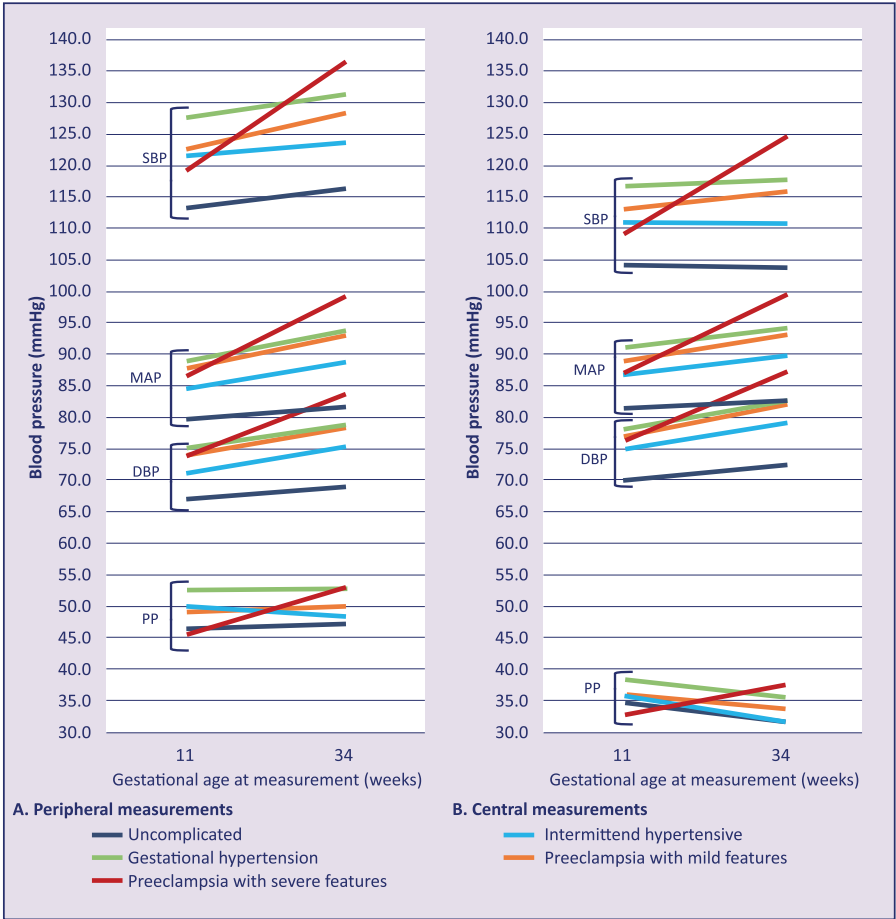

Figure 1. Means of peripheral (A) and central (B) measurements at 11 and 34 weeks of gestation for different HDP groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, PP, pulse pressure.
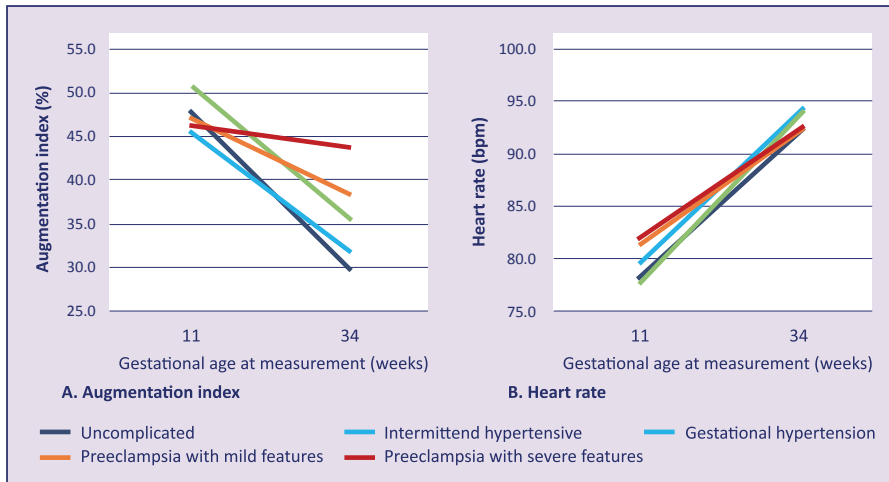
Figure 2. Means of augmentation index (A) and heart rate (B) at 11 and 34 weeks' gestation for different HDP groups.

At 34 weeks' gestation, women with uncomplicated pregnancies showed mean pSBP 116.1mmHg, pDBP 68.9mmHg, pPP 47.2mmHg, pMAP 81.6mmHg, cSBP 103.8mmHg, cDBP 72.3mmHg, cPP 31.5mmHg, cMAP 82.8mmHg, AIx 29.8% and HR 92.6bpm. At 34 weeks', women from all HDP groups showed significantly increased mean pSBP, pDBP, pMAP, cSBP, cDBP and cMAP compared to those with uncomplicated pregnancies. An increased pPP at 34 weeks' was seen in those who subsequently developed GH, but not in those who developed sPE, nsPE or IH. Furthermore, cPP was increased in those who later develop GH and sPE, but not in those who developed nsPE and IH, compared to those with uncomplicated pregnancies. AIx was increased in women who developed nsPE (38.4%, p=0.007) and sPE (43.8%, p=0.040). There were no differences between HDP groups in PR at 34 weeks'.

Maternal haemodynamics across gestation in HDP groups.
Across gestation, regardless of HDP group, there was a mean increase in pSBP (2.9mmHg), pDBP (2.1mmHg) and pMAP (1.8mmHg), cDBP (2.4mmHg), cMAP (1.4mmHg), HR (14.5bpm) and a mean decrease in cPP (-2.9mmHg) and AIx (18.2%) while pPP and cSBP did not change (Supplementary Table 1 and 2).
After adjusting for baseline measurement, maternal age and BMI, women who developed sPE showed a significant additional increase in pSBP, pDBP, pMAP, pPP, cSBP, cDBP, cMAP and cPP compared to those with uncomplicated pregnancies (Figure 3). Women who developed nsPE showed a significant additional increased pDBP, pMAP, cSBP, cDBP and cMAP, but not pSBP, pPP and cPP, compared to uncomplicated pregnancies. The change across gestation, after adjustment, for pSBP, pDBP, pMAP, pPP, cSBP, cDBP, cMAP and cPP in women who developed GH and IH was not different from those with uncomplicated pregnancies. The adjusted AIx decrease was lower in women who developed sPE (15.5%) and nsPE (9.0%), while the GH and IH women demonstrated a similar AIx decrease to uncomplicated pregnancies (Figure 4). The increase in HR across gestation in each HDP group was similar to uncomplicated pregnancies.

Table 2. Means of haemodynamic parameters at 11 and 34 weeks of gestation for different HDP groups

	Uncomplicated		IH		GH		nsPE		sPE	
	Mean ±SD	Adj p	Mean ±SD	Adj p	Mean ±SD	Adj p	Mean ±SD	Adj p	Mean ±SD	Adj p
Assessment at 11+2 weeks'										
pSBP	113.3 ±10.1	Ref	121.5 ±10.9	0.000	127.6 ±12.2	0.000	123.1 ±12.7	0.000	119.4 ±10.3	0.514
pDBP	66.9 ±7.4	Ref	71.3 ±7.5	0.017	75.1 ±8.7	0.000	73.9 ±7.7	0.000	73.8 ±9.0	0.020
pPP	46.4 ±8.8	Ref	50.2 ±7.5	0.190	52.6 ±9.8	0.008	49.2 ±9.3	0.399	45.6 ±5.1	1.000
pMAP	79.8 ±7.7	Ref	84.6 ±8.3	0.012	89.2 ±9.2	0.000	87.8 ±8.9	0.000	86.8 ±9.5	0.036
cSBP	104.3 ±9.5	Ref	110.9 ±9.5	0.003	116.7 ±11.8	0.000	113.2 ±10.6	0.000	109.2 ±9.3	0.934
cDBP	69.9 ±7.4	Ref	74.8 ±7.5	0.005	78.4 ±8.5	0.000	77.1 ±7.8	0.000	76.4 ±9.0	0.038
cPP	34.4 ±7.0	Ref	36.1 ±5.9	1.000	38.4 ±7.3	0.060	36.1 ±6.5	1.000	32.8 ±3.4	1.000
cMAP	81.4 ±7.4	Ref	86.9 ±7.7	0.001	91.2 ±9.1	0.000	89.1 ±8.3	0.000	87.3 ±8.9	0.093
AIx	48.0 ±17.7	Ref	45.7 ±15.5	1.000	50.8 ±14.4	1.000	47.3 ±20.0	1.000	46.6 ±13.9	1.000
HR	78.1 ±11.1	Ref	79.5 ±12.8	1.000	77.6 ±9.3	1.000	81.4 ±12.2	0.619	81.9 ±14.4	1.000
Assessment at 34+2 weeks'										
pSBP	116.1 ±10.2	Ref	123.8 ±10.6	0.001	131.4 ±11.9	0.000	128.3 ±12.8	0.000	136.7 ±10.3	0.000
pDBP	68.9 ±7.7	Ref	75.4 ±8.6	0.000	78.8 ±8.4	0.000	78.5 ±9.0	0.000	83.6 ±11.3	0.000
pPP	47.2 ±7.2	Ref	48.4 ±7.4	1.000	52.7 ±8.8	0.006	49.8 ±8.2	0.226	53.1 ±6.1	0.074
pMAP	81.6 ±8.0	Ref	88.8 ±9.7	0.000	93.8 ±8.1	0.000	93.0 ±10.8	0.000	99.2 ±11.8	0.000
cSBP	103.8 ±9.4	Ref	110.8 ±8.6	0.002	117.8 ±11.8	0.000	115.6 ±11.9	0.000	124.5 ±11.9	0.000
cDBP	72.3 ±7.9	Ref	79.2 ±8.4	0.000	82.3 ±8.7	0.000	81.9 ±8.9	0.000	87.0 ±10.8	0.000
cPP	31.5 ±5.8	Ref	31.6 ±4.7	1.000	35.4 ±7.1	0.019	33.8 ±6.2	0.136	37.5 ±5.5	0.006
cMAP	82.8 ±8.0	Ref	89.7 ±8.2	0.000	94.1 ±9.2	0.000	93.1 ±9.6	0.000	99.5 ±10.9	0.000
AIx	29.8 ±15.3	Ref	31.9 ±15.5	1.000	35.6 ±18.2	1.000	38.4 ±21.2	0.948	43.8 ±21.3	0.040
HR	92.6 ±14.8	Ref	94.6 ±14.6	1.000	94.2 ±11.6	1.000	92.4 ±13.8	1.000	92.7 ±12.9	1.000

IH, intermittent hypertensive; GH, gestational hypertension; nsPE, preeclampsia without severe features; sPE, preeclampsia with severe features; pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure; pPP, peripheral pulse pressure; pMAP, peripheral mean arterial pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cMAP, central mean arterial pressure; AIx, augmentation index; HR, heart rate. All HDP groups were compared to uncomplicated pregnancies (reference group). The reported p-values are Bonferroni adjusted.
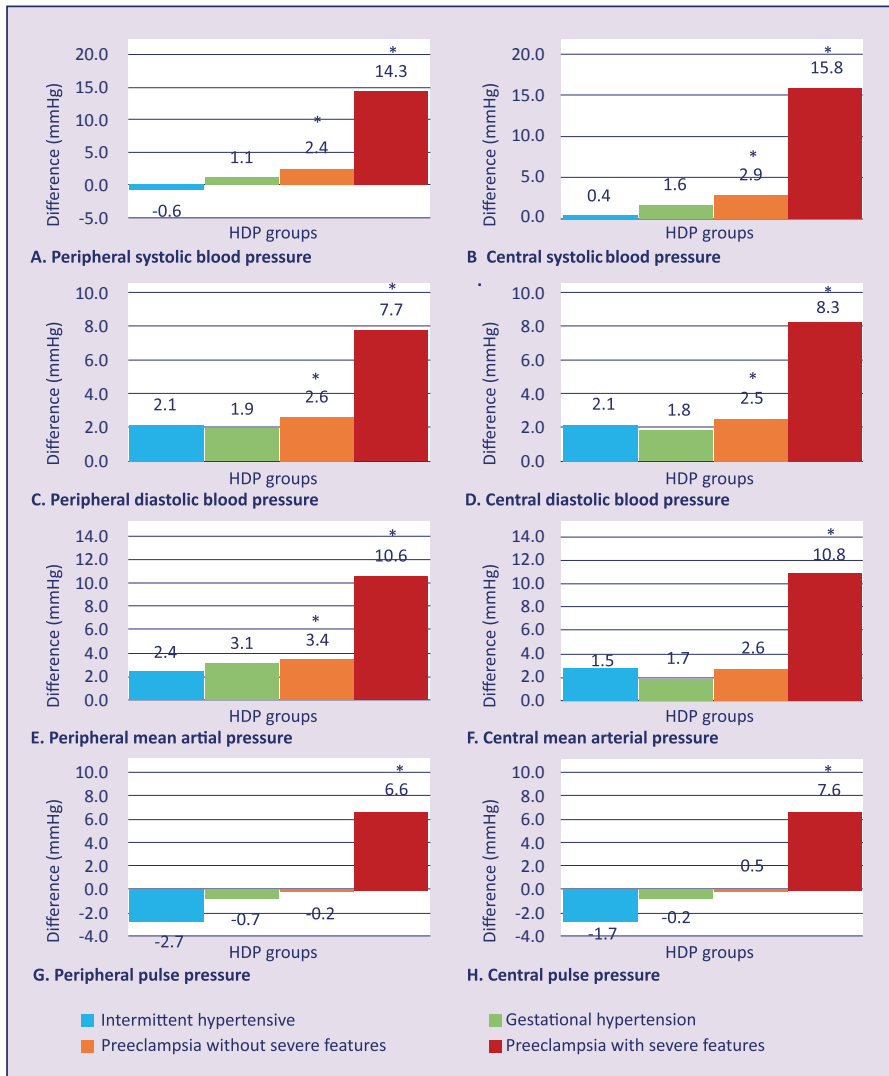
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Figure 3. Differences in estimated marginal means in blood pressure across gestation in each hypertensive disorder of pregnancy (HDP) group. Data are presented as corrected mean difference (mmHg) across gestation compared to uncomplicated pregnancies. 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 (28.2kg/m^2) and their mean baseline measurement [pSBP: 116.2mmHg (A); pDBP: 68.8mmHg (C), pMAP: 81.9mmHg (E); pPP: 47.7mmHg (G); cSBP: 105.9mmHg (B); cDBP: 71.4mmHg (D); cMAP: 82.9mmHg (F); cPP: 34.6mmHg(H)].
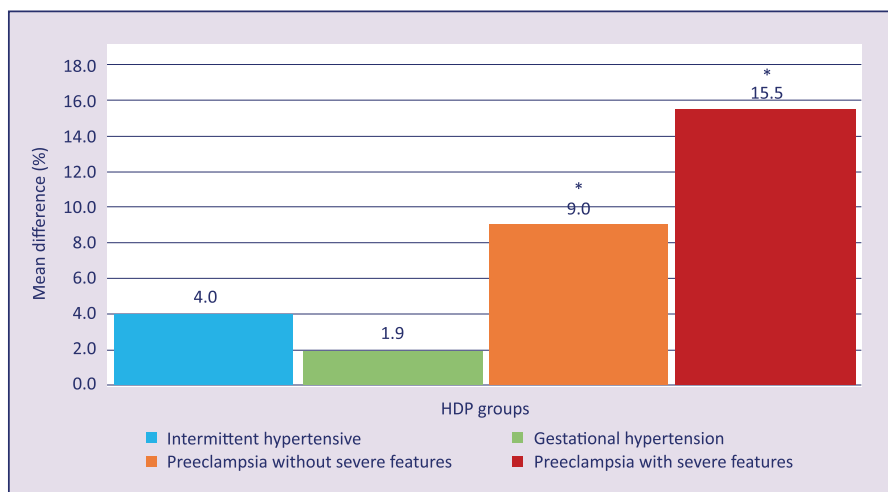
Figure 4. Differences in estimated marginal means in augmentation index across gestation in each hypertensive disorder of pregnancy (HDP) group. Data are presented as mean difference in augmentation index (AIx in %) compared to women with uncomplicated pregnancies. Values with an asterix indicate significant 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 (28.2kg/m^2) and baseline measurement (47.9%).

Discussion

This study observed differences in haemodynamic parameters at 11 weeks' and 34 weeks' gestation and across gestation in women who developed HDP, compared to women with uncomplicated pregnancies.

Maternal haemodynamics in pregnancies complicated by HDP

Compared to women with uncomplicated pregnancies, those who developed sPE had increased pDBP, pMAP and cDBP at 11 weeks', while pSBP, pDBP, pMAP, 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. Women who developed nsPE had increased pSBP, pDBP, pMAP, pPP, cSBP, cDBP and cMAP at 11 weeks', while pSBP, pDBP, pMAP, cSBP, cDBP, cMAP and AIx were increased at 34 weeks'. Across gestation they had an increased adjusted mean difference for pDBP, pMAP, 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, indicating this is often essential hypertension diagnosed during pregnancy.

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Women with IH 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 uncomplicated pregnancies. This suggests that women who develop IH 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 IH suggests that IH is not a benign condition, a risk often not recognized by clinicians.

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 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[11], and cost-effectively[17], in addition to the previous mentioned benefits, it should be considered in the clinic for the monitoring of women at risk of HDP.

AIx is considered to be a measure of arterial stiffness, influenced by wave reflections from the arterial vessel tree[18,19]. 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[18]. 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[18]. 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 the GH and IH women 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[20–22].

Strengths and limitations
A strength of this study is its prospective character and extensive amount of data collected on a low-risk population. 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.

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 IH had elevated haemodynamic parameters in first and

third trimester and higher risk of SGA, indicating that IH 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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Supplementary table 1: Summary of linear mixed-effect models for peripheral and central measurements

Characteristic	pSBP estimate (95% CI)	pDBP estimate (95% CI)	pMAP estimate (95% CI)	pPP estimate (95% CI)
Intercept	30.96 (25.08 to 36.83)	14.67 (10.90 to 18.43)	20.5 (15.94 to 25.07)	16.82 (13.65 to 20.00)
Mean difference between measurements (all groups)	2.92 (1.76 to 4.07)	2.05 (1.16 to 2.93)	1.82 (0.84 to 2.79)	0.87 (-0.04 to 1.78)
Mean Uncomplicated*	Reference group	Reference group	Reference group	Reference group
Mean Intermittent hypertensive*	2.08 (-0.47 to 4.63)	1.03 (-0.92 to 2.98)	1.20 (-0.96 to 3.35)	1.10 (-0.90 to 3.09)
Mean Gestational hypertension*	3.52 (0.58 to 6.46)	1.83 (-0.40 to 4.07)	2.27 (-0.21 to 4.74)	1.71 (-0.57 to 3.99)
Mean Pre-eclampsia with mild features*	2.36 (0.17 to 4.55)	1.65 (-0.03 to 3.33)	2.05 (0.19 to 3.91)	0.59 (-1.11 to 2.28)
Mean Pre-eclampsia with severe features*	1.36 (-2.70 to 5.41)	1.61 (-1.51 to 4.73)	1.73 (-1.71 to 5.18)	-0.58 (-3.76 to 2.61)
Mean difference uncomplicated pregnancies**	Reference group	Reference group	Reference group	Reference group
Mean difference intermittent hypertensive**	-0.57 (-4.17 to 3.02)	2.13 (-0.63 to 4.89)	2.38 (-0.66 to 5.43)	-2.69 (-5.51 to 0.14)
Mean difference gestational hypertension**	1.15 (-2.94 to 5.23)	1.91 (-1.23 to 5.05)	3.10 (-0.37 to 6.56)	-0.73 (-3.95 to 2.48)
Mean difference pre-eclampsia without severe features**	2.42 (-0.61 to 5.45)	2.58 (0.25 to 4.90)	3.39 (0.83 to 5.96)	-0.16 (-2.54 to 2.22)
Mean difference pre-eclampsia with severe features**	14.33 (8.61 to 20.05)	7.70 (3.31 to 12.09)	10.6 (5.75 to 15.45)	6.63 (2.13 to 11.1)
Baseline measurement	0.69 (0.64 to 0.75)	0.73 (0.68 to 0.78)	0.69 (0.64 to 0.75)	0.63 (0.59 to 0.68)
Maternal age	-0.04 (-0.15 to 0.07)	0.07 (-0.01 to 0.15)	0.04 (-0.05 to 0.13)	-0.12 (-0.21 to -0.04)
Maternal body mass index	0.17 (0.09 to 0.26)	0.07 (0.01 to 0.12)	0.11 (0.04 to 0.17)	0.12 (0.06 to 0.18)

Characteristic	cSBP estimate (95% CI)	cDBP estimate (95% CI)	cMAP estimate (95% CI)	cPP estimate (95% CI)
Intercept	26.94 (21.64 to 32.23)	15.42 (11.51 to 19.33)	18.16 (13.87 to 22.45)	11.71 (9.23 to 14.18)
Mean difference between measurements (all groups)	-0.50 (-1.59 to 0.59)	2.35 (1.47 to 3.24)	1.40 (0.51 to 2.29)	-2.86 (-3.61 to -2.11)
Mean Uncomplicated*	Reference group	Reference group	Reference group	Reference group
Mean Intermittent hypertensive*	1.62 (-0.78 to 4.02)	1.1 (-0.85 to 3.04)	1.20 (-0.76 to 3.16)	0.49 (-1.15 to 2.14)
Mean Gestational hypertension*	2.99 (0.22 to 5.75)	1.8 (-0.43 to 4.04)	2.07 (-0.18 to 4.33)	1.19 (-0.69 to 3.07)
Mean Pre-eclampsia with mild features*	2.13 (0.06 to 4.19)	1.6 (-0.08 to 3.28)	1.68 (-0.01 to 3.37)	0.42 (-0.98 to 1.83)
Mean Pre-eclampsia with severe features*	1.03 (-2.80 to 4.85)	1.43 (-1.68 to 4.54)	1.25 (-1.88 to 4.37)	-0.73 (-3.37 to 1.90)
Mean difference uncomplicated pregnancies**	Reference group	Reference group	Reference group	Reference group
Mean difference intermittent hypertensive**	0.37 (-3.03 to 3.76)	2.12 (-0.63 to 4.87)	1.53 (-1.23 to 4.30)	-1.74 (-4.07 to 0.60)
Mean difference gestational hypertension**	1.59 (-2.27 to 5.44)	1.84 (-1.29 to 4.97)	1.75 (-1.39 to 4.89)	-0.22 (-2.88 to 2.43)
Mean difference pre-eclampsia without severe features**	2.94 (0.08 to 5.80)	2.46 (0.15 to 4.78)	2.62 (0.29 to 4.95)	0.48 (-1.49 to 2.45)
Mean difference pre-eclampsia with severe features**	15.83 (10.43 to 21.22)	8.26 (3.89 to 12.64)	10.79 (6.39 to 15.19)	7.57 (3.85 to 11.28)
Baseline measurement	0.71 (0.66 to 0.76)	0.74 (0.69 to 0.79)	0.74 (0.69 to 0.80)	0.64 (0.59 to 0.69)
Maternal age	0.00 (-0.10 to 0.11)	0.03 (-0.05 to 0.11)	0.02 (-0.06 to 0.10)	-0.02 (-0.09 to 0.05)
Maternal body mass index	0.11 (0.04 to 0.19)	0.07 (0.01 to 0.13)	0.08 (0.02 to 0.14)	0.05 (0.00 to 0.10)

pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure; pMAP, peripheral mean arterial pressure; pPP, peripheral pulse pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; cMAP, central mean arterial pressure; cPP, central pulse pressure. Data are presented as Estimates (95%-Confidence interval). Values in bold indicate significant estimates. Estimates in the model were corrected for mean maternal age (26.07 years), mean maternal BMI (28.17kg/m2) and their mean baseline measurement (pSBP: 116.2 mmHg; pDBP: 68.8 mmHg, pMAP: 81.9 mmHg; pPP: 47.4 mmHg; cSBP: 105.9 mmHg; cDBP: 71.4 mmHg; cMAP: 82.9 mmHg; cPP: 34.6 mmHg). Intercepts were random for each characteristic. *, Mean of the two measurements together per HDP group compared to uncomplicated pregnancies. **, Mean difference between the two measurements per HDP group compared to uncomplicated pregnancies

Supplementary table 2: Summary of multilevel linear mixed-effect models for augmentation index and pulse rate

Characteristic	AIx Estimate (95%-CI)	HR Estimate (95%-CI)
Intercept (random)	**10.87 (5.36 to 16.30)**	**22.95 (15.82 to 30.08)**
Mean difference between measurements (all groups)	**-18.23 (-20.08 to -16.38]**	**14.54 (12.94 to 16.13)**
Mean Uncomplicated*	Reference group	Reference group
Mean Occasionally hypertensive*	-0.55 (-4.60 to 3.50)	0.08 (-3.41 to 3.57)
Mean Gestational hypertension*	1.00 (-3.63 to 5.63)	-0.71 (-4.69 to 3.27)
Mean Pre-eclampsia with mild features*	0.02 (-3.44 to 3.47)	0.41 (-2.57 to 3.39)
Mean Pre-eclampsia with severe features*	-0.39 (-6.89 to 6.10)	0.80 (-4.79 to 6.39)
Mean difference uncomplicated**	Reference group	Reference group
Mean difference occasionally hypertensive**	4.03 (-1.73 to 9.79)	0.80 (-4.15 to 5.76)
Mean difference gestational hypertension**	1.93 (-4.62 to 8.48)	2.62 (-3.01 to 8.26)
Mean difference pre-eclampsia with mild features**	**9.00 (4.15 to 13.86)**	-3.22 (-7.40 to 0.95)
Mean difference pre-eclampsia with severe features**	**15.48 (6.32 to 24.65)**	-3.79 (-11.67 to 4.10)
Baseline measurement	**0.71 (0.66 to 0.76)**	**0.72 (0.66 to 0.79)**
Maternal age	**0.18 (0.00 to 0.37)**	**-0.21 (-0.36 to -0.05)**
Maternal body mass index	-0.07 (-0.18 to 0.05)	**0.15 (0.05 to 0.25)**

AIx, augmentation index; HR, heart rate. Data are presented as Estimates (95%-Confidence interval).
Estimates in the model were corrected for mean maternal age (26.1 years), mean maternal BMI (28.2kg/m2)
and their mean baseline measurement (AIx: 47.9%, HR: 78.7 bpm).
Intercepts were random for each characteristic.
*, Mean of the two measurements together per HDP group compared to uncomplicated pregnancies.
**, Mean difference between the two measurements per HDP group compared to uncomplicated pregnancies

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