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ORIGINAL RESEARCH

Recognizing Cardiovascular Risk After Preeclampsia: The P4 Study

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BACKGROUND: There is increased risk of hypertension, early cardiovascular disease, and premature mortality in women who have had preeclampsia. This study was undertaken to determine the upper limit of normal blood pressure (BP) 6 months postpartum and the frequency of women with prior preeclampsia who had BP above these limits, as part of the P4 (Post-Partum Physiology, Psychology and Pediatric) follow-up study.

METHODS AND RESULTS: BP was measured by sphygmomanometer, 24-hour ambulatory BP monitoring, and non-invasive central BP at 6 months postpartum in 302 women who had normotensive pregnancy and 90 who had preeclampsia. The upper limit of normal BP (mean+2 SD) for women with normotensive pregnancy was 122/79 mm Hg for routine BP, 115/81 mm Hg for central BP, and 121/78 mm Hg for 24-hour ambulatory BP monitoring. Traditional normal values detected only 3% of women who had preeclampsia as having high BP 6 months postpartum whereas these new values detected between 13% and 19%. Women with preeclampsia had greater body mass index (27.8 versus 25.0, $P<0.001$) and left ventricular wall thickness but similar augmentation index. They also had lower high-density lipoprotein (59±15 versus 65±16 mg/dL, $P=0.002$), higher triglycerides (77±51 versus 61±35 mg/dL, $P=0.005$), and higher homeostatic model assessment score (2.1±1.8 versus 1.3±1.9, $P<0.001$).

CONCLUSIONS: Clinicians wishing to detect high BP in these women should be aware of the lower than usual upper limit of normal for this young cohort and where possible should use 24-hour ambulatory BP monitoring to detect these changes. This may define a subgroup of women who had preeclampsia for whom targeted BP lowering therapy would be successful.

REGISTRATION: URL: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=365295&isReview=true; Unique identifier: ACTRN12613001260718.

Key Words: blood pressure monitoring ■ cardiovascular risk ■ high blood pressure ■ preeclampsia ■ pregnancy hypertension

It is well recognized that women who have had preeclampsia have increased risk for cardiovascular disease, diabetes mellitus, renal disease, and premature death compared with women who have had normotensive pregnancies.[1–11] Although this association has been recognized for many years, only recently has preeclampsia become listed as an independent risk factor for cardiac disease.[12] The rate at which women are hospitalized with myocardial infarction is rising, not easily predicted by traditional cardiovascular risk factors,[13] and preeclampsia is probably a contributor to this risk. Indeed, women with preexisting essential hypertension, diabetes mellitus, or obesity are recognized as being at increased risk both for preeclampsia[14] and later life cardiovascular disease.

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CLINICAL PERSPECTIVE

What Is New?

- The upper limit of normal blood pressure (BP) 6 months postpartum for women with normotensive pregnancy was lower than values traditionally considered upper normal.
- Using traditional upper limits of normal BP detected high BP in only 3% of women who had preeclampsia 6 months postpartum, whereas using these new values detected between 13% and 19%.
- Our data suggest that women who have had preeclampsia have a high frequency of features consistent with early vascular aging.

What Are the Clinical Implications?

- All these findings have direct relevance to the postpartum investigation and management of women who have had preeclampsia and should help shape efforts to prevent their longer-term cardiovascular risk.
- Applying new upper normal limits of BP for young women may define a subgroup of women who have had preeclampsia for whom targeted BP lowering therapy would be appropriate.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
EVA	early vascular aging
HOMA	homeostatic model assessment

Women are at least as likely as men to develop cardiovascular disease but healthcare providers are not always aware of preeclampsia being a significant risk factor.[15] Even when women are assessed for their cardiovascular risk after a preeclamptic pregnancy clinicians (understandably) use traditional cut-off values for risk factors such as blood pressure (BP) when assessing these women. Problems arise firstly in that learned groups differ in their criteria (either 130/80 or 140/90 mm Hg) for defining hypertension,[16,17] and secondly that these normal values, and the benefits of anti-hypertensive treatment, have not been derived from cohorts of young parous women, but more typically from older cohorts, and predominantly men.[18]

We therefore undertook this prospective study 6 months after pregnancy to (1) define what constitutes "normal" for BP in young women, and (2) determine the proportion of women who had preeclampsia with BP and other cardiovascular risk factors that lay outside both traditional and these new normal ranges, so as to heighten clinicians' attention to potential risk for such women.

METHODS

Study Design, Population, and Recruitment

The data that support the findings of this study are available from the corresponding author upon reasonable request. Detailed study methodology of the P4 (Postpartum Physiology, Psychology, and Pediatric) follow-up study, has been published previously.[19] Women who had delivered following a normotensive pregnancy and women who had a preeclamptic pregnancy were invited to participate. Preeclampsia was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy.[20]

Women attended ≈6 months post-partum to have their BP assessed peripherally with a liquid crystal sphygmomanometer[21] and 24-hour ambulatory blood pressure monitoring (ABPM), and centrally using non-invasive applanation tonometry at the radial artery. ABPM was chosen over home BP monitoring as it is considered the best method of assessing BP.[22] Additional testing included echocardiography (with blinded reporting by a cardiologist); liver and renal function; lipids, renin, and aldosterone and urinary albumin; fasting glucose and insulin (with derivation of the homeostatic model assessment (HOMA) score to assess insulin resistance[23]); and urinalysis. Body mass index (BMI), BP, HOMA score, triglycerides, and high-density lipoprotein cholesterol were used to assess metabolic syndrome and central BP, and HOMA scores were used as markers of early vascular aging (EVA).

Statistical Analysis

Data were analyzed using SPSS version 25. Comparisons between groups were tested using Student independent *t*-test for normally distributed continuous variables and Chi-square testing for categorical variables. The primary outcome was the prevalence of women who formerly had preeclampsia with mean 24-hour systolic or diastolic BP >2 SD greater than the mean BP derived from women who had normotensive pregnancies. The study was powered on the proportion of 24-hour mean diastolic BP readings ≥2 SD above the mean for women who were normotensive in pregnancy, with preliminary data that suggested 56 women after preeclampsia and normotensive pregnancy would be required to

assess this with 85% power (α=0.05). For appropriate power to construct a normal range (95% reference range) for BP 6 months postpartum, 292 women post-normotensive pregnancy were required[19] and to accommodate potential dropouts we recruited 90 women with preeclampsia. Because of multiple comparisons made between groups, apart from the primary outcomes (considered significant at P=0.05), after using a Bonferroni correction only a $P \leq 0.005$ was considered statistically significant.

The study was approved by the South Eastern Sydney Local Health District Ethics committee. All women gave written informed consent.

RESULTS

We studied 302 women after normotensive pregnancy, who represented 11% of those invited (302 of 2754), and 90 women who had preeclampsia, 62% of those invited (90 of 145). Studies were undertaken at an average of 27 (SD, 1.3) weeks postpartum.

Baseline Characteristics of Participants and Non-Participants

Women with normotensive pregnancies who consented to participate in this study (n=302) were slightly older (average, 33 versus 31 years; P<0.001), had slightly higher BP (average, 108/67 versus 101/62 mm Hg; P<0.001) in their first trimester, and were more likely to have had a normal vaginal birth than women who did not consent (n=2452) (P<0.001), but did not differ in gestation at birth (39 weeks). Women with preeclampsia who consented to the study (n=90) were similar in age, BMI, first trimester BP, and gestation at birth as those who did not participate (n=55) but were more likely to have received intravenous magnesium sulfate (24% versus 4%, P=0.001) (Table S1).

Baseline Characteristics of Women With Normotensive and Preeclamptic Pregnancies

Women with preeclampsia were more likely primiparous, had greater BMI, and had slightly higher BP at the start of their pregnancy (10 weeks of gestation) upon referral from their primary care physician (P=0.002) than women who had a normotensive pregnancy (Table 1). This BP difference was also present at their first visit to the hospital, on average at 16 weeks of gestation (P<0.001). There was no difference in frequency of smokers between groups. Women withpreeclampsia gave birth earlier (37 versus 39 weeks, P<0.001) with more babies born preterm (33% versus 6%), and more babies born small for gestational age (24% versus 7%, P<0.001).

BP at 6 Months

The average routine sphygmomanometry BP 6 months postpartum for women who had a normotensive pregnancy was 104/66 mm Hg with an upper limit of normal 122/79 mm Hg (Figure 1). Women who had preeclampsia had average BP significantly higher than that of women who had normotensive pregnancies whether measured routinely (113/72 mm Hg) or as central BP, awake, sleep or 24-hour mean BP (all P<0.001).

Awake, sleep, and 24-hour pulse pressures (all P<0.001) and central pulse pressure (P=0.021) were significantly higher 6 months postpartum in women who had preeclampsia. Twenty-four-hour (73 versus 76 bpm, P=0.002), awake (77 versus 80 bpm, P=0.002), and sleep average heart rates (63 versus 67 bpm, P<0.001) were also significantly higher 6 months postpartum in women who had preeclampsia.

Routine systolic BP fell by 4 mm Hg between 10 weeks of gestation and 6 months postpartum in women who had normotensive pregnancies (P<0.001) but diastolic BP was unchanged. Women who had preeclampsia had no change in routine BP between 10 weeks of gestation and 6 months postpartum (Table 2).

Cardiovascular Risk Factors 6 Months Postpartum

Women with preeclampsia still had slightly greater BMI than those who had normotensive pregnancy (BMI, 27.8 versus 25.0, P<0.001), having begun their pregnancies that way (Table 2). High-density lipoprotein was slightly lower and triglycerides higher along with higher insulin and HOMA score (P<0.001) but hemoglobin A1c was similar. Plasma renin, aldosterone, and aldosterone/renin ratio were similar between groups as was serum creatinine and estimated glomerular filtration rate. Although serum uric acid and urinary albumin/creatinine were slightly higher in those with preeclampsia this was not statistically significant when accounting for multiple comparisons. Augmentation index was similar between groups (mean 23% in both groups).

Echocardiographic Findings at 6 Months

Echocardiography was obtained in 74 women who had normotensive pregnancies and 44 who had preeclampsia (Table 3). Women with previous preeclampsia had significantly greater septal and posterior wall thickness and left ventricular mass as well as lower mitral E/A ratio and higher E/E′ ratios, consistent with more diastolic dysfunction 6 months postpartum, even though these measurements lie within traditionally “normal” ranges.

Table 1. Baseline Characteristics of Women Who Had Normotensive Pregnancy and Those Who Had Preeclampsia

	Normotensive			Preeclampsia			
	n	Mean	SD	n	Mean	SD	*P* Value
BMI at booking	302	24	5	90	26	5	0.003
Gestation at booking BP (wk) with GP	281	10	5	73	10	5	0.237
Booking GP SBP, mm Hg	281	108	11	74	113	12	0.002
Booking GP DBP, mm Hg	281	67	8	74	71	8	<0.001
Gestation at hospital booking BP, wk	276	15	4	81	16	4	0.243
Hospital booking SBP, mm Hg	276	103	10	82	109	10	<0.001
Hospital booking DBP, mm Hg	276	63	7	82	67	9	<0.001
Gestation at birth, wk	302	39	2	90	37	3	<0.001
Birth weight (baby), g	302	3367	511	90	2753	733	<0.001
Maternal age, y	302	33	5	90	32	5	0.016
Apgar, 1 min	300	9	1	90	8	2	<0.001
Apgar, 5 min	300	9	1	90	9	1	0.003
	Normotensive (%) n=302			Preeclampsia (%) n=90			*P* Value
Primigravidas	50			73			<0.001
Episodes of severe hypertension (≥160/110)	0			38			<0.001
Preterm birth (<37 wk)	6			33			<0.001
SGA (<10th percentile)	7			24			<0.001
Vaginal birth	81			51			<0.001
Magnesium Sulfate given	0			24			<0.001
Education							
Secondary	9			4			0.044
Diploma	23			36			
University degree	68			60			
Smoker							
Never	67			61			0.193
Former	28			29			
Current	5			10			
Labor onset							
Spontaneous	58			9			<0.001
Induced	32			66			
No labor	10			26			
Background/Ethnicity/Race							
White	54			52			0.152
Asian	22			20			
ATSI	0.7			2			
Polynesian	0.3			3			
European	14			12			
Other	9			10			
Breastfeeding on discharge							
Yes	94			86			0.012
No	3			3			
Both breast and bottle	3			11			

"Booking" is the gestation at first presentation to the primary care physician or hospital clinic. ATSI indicates Aboriginal and Torres Strait Islander; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GP, general practitioner/primary care physician; SBP, systolic blood pressure; and SGA, small for gestational age.

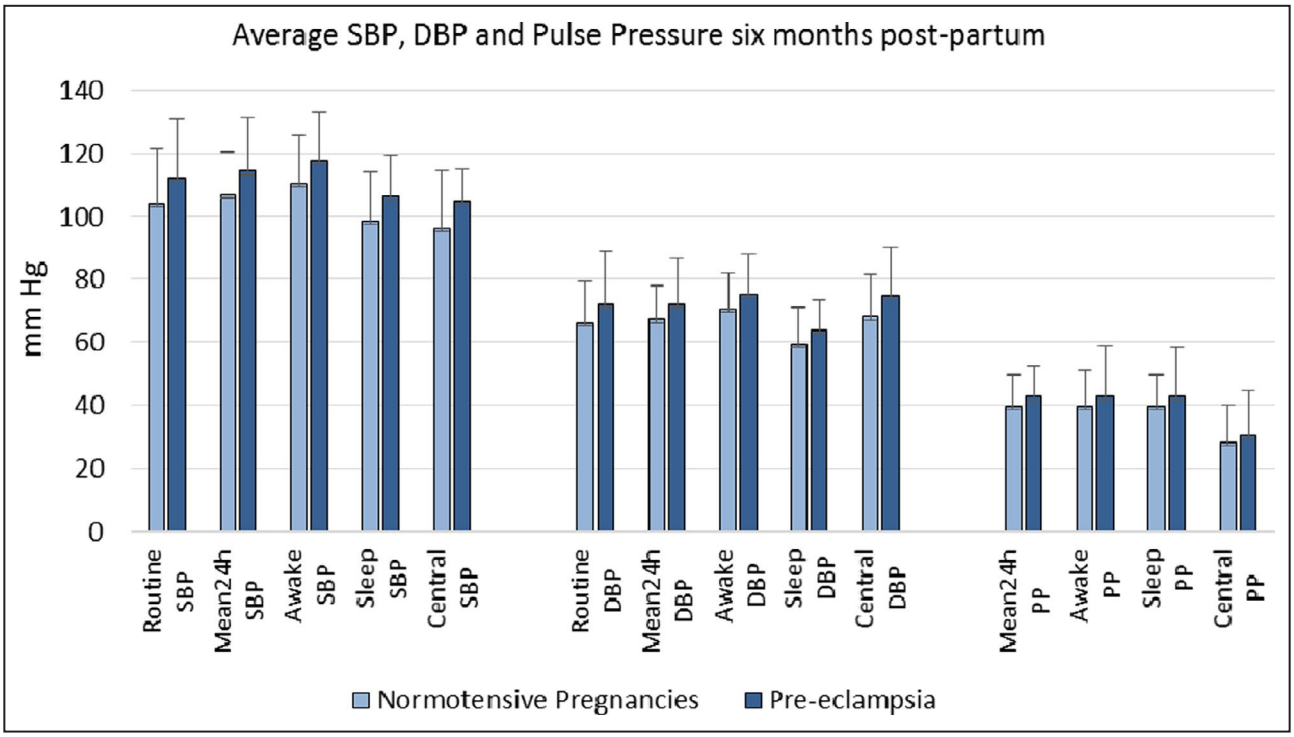


Figure 1. Routine sphygmomanometry and ambulatory awake, sleep, and central systolic and diastolic blood pressures and pulse pressures 6 months postpartum.
All measurements were significantly higher in women who had preeclampsia, $P<0.001$. DBP indicates diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.

Normal BP 6 Months Postpartum

The upper limits of normal for young parous women 6 months postpartum were 122/79 mm Hg for routine BP, 115/81 mm Hg for central BP, 121/78 mm Hg for 24-hour ambulatory BP, 126/82 mm Hg for awake ABPM and 114/71 mm Hg for sleep BP.

Women Who Had Preeclampsia With High BP at 6 Months

BP in women who had preeclampsia was compared against both a "Traditional" upper normal threshold value for routine BP of 139 mm Hg systolic and 89 mm Hg diastolic[16] and also against upper threshold values of 129 mm Hg systolic and 79 mm Hg diastolic to account for more recent recommendations of the American College of Cardiology/American Heart Association[17] (Figure 2). Central systolic BP of 119 mm Hg was considered the upper normal and mean 24-hour ABPM blood pressure <130/80 mm Hg was considered traditionally normal.[24]

Using a traditional cut-off defining hypertension by routine sphygmomanometry BP as ≥140/90 mm Hg detected only 3% of women with preeclampsia as having high BP whereas 13% to 19% were considered abnormal using the new normal range defined within this study for young women 6-months postpartum.

Central BP measurement offered only a small change in frequency of detection, detecting 8% with traditional levels and 12% using the new cut-off level. Twenty-four--hour ABPM increased detection of high BP from 2% to 19% for systolic BP and 11% to 19% for diastolic BP using the newly defined range for normal women in this study rather than traditional ranges and ABPM diagnosed high BP more often than routine sphygmomanometry measurement. Seventeen of the 90 women who had preeclampsia had 24-hour ABPM systolic BP above the new normal range determined in this study but only 6 of these women had routine sphygmomanometer systolic BP above the new normal range. Only 2 women who had preeclampsia had 24-hour ABPM systolic BP above traditionally normal ABPM values and neither of these had routine systolic BP above traditional normal values. Nine of the 90 women with preeclampsia had 24-hour ABPM systolic BP above normal values as more recently defined by American College of Cardiology/American Heart Association but none of these women had routine systolic BP above normal as defined by American College of Cardiology/American Heart Association. Similar results were found when hypertension was defined solely by awake ABPM rather than by 24-hour ABPM (Table S2).

Table 2. Renal and Liver Function, Blood Count, Lipids, Insulin Resistance, Vitamin D, and Change in Systolic and Diastolic Blood Pressure From the First Trimester to 6 Months Postpartum

	Normotensive			Preeclampsia			
	n	Mean	SD	n	Mean	SD	*P* Value
BMI	302	25.0	5.1	90	27.8	5.9	<0.001
Creatinine, mg/dL	299	0.7	0.1	89	0.7	0.1	0.225
eGFR, mL/min	299	95.0	8.9	89	96.7	7.7	0.075
ALP, IU	299	77.5	21.3	87	83.3	20.6	0.024
GGT, IU	299	14.5	14.5	87	20.0	24.4	0.044
ALT, U/L	299	19.7	9.2	87	21.1	11.4	0.314
AST, U/L	298	19.8	5.2	85	20.9	5.7	0.118
Glucose, mg/dL	299	83.7	7.6	89	85.8	7.0	0.014
Urate, mg/dL	299	4.6	1.0	88	4.9	1.1	0.020
White cell count, 10^9/L	297	5.3	1.2	89	5.8	1.8	0.022
Hemoglobin, g/dL	297	13.2	0.8	89	13.0	1.0	0.042
Platelets, 10^9/L	296	247.3	53.3	88	260.0	59.1	0.073
Cholesterol, mg/dL	299	177.6	27.6	88	180.5	34.1	0.469
LDL, mg/dL	299	100.4	26.3	88	105.6	30.6	0.149
HDL, mg/dL	299	65.2	15.7	89	59.4	14.7	0.002
Triglyceride, mg/dL	299	60.8	34.6	88	77.4	50.9	0.005
Aldosterone, ng/dL	298	9.0	6.4	87	10.8	9.4	0.093
Renin, mU/L	296	17.0	13.3	84	16.2	11.0	0.553
Aldosterone:renin ratio	296	21.6	25.6	84	33.2	75.6	0.173
Insulin, mU/L	298	6.1	7.7	88	9.6	8.2	0.001
HbA1c, %	298	5.2	0.3	89	5.2	0.3	0.946
Vitamin D, ng/mL	299	27.8	8.5	88	27.3	7.4	0.561
HOMA score	298	1.3	1.9	88	2.1	1.8	0.001
Urine albumin/creatinine, mg/g	297	10.5	31.4	88	19.6	27.9	0.010
Difference between 6-m routine SBP and first trimester SBP	279	−3.9	11.8	73	−0.9	10.1	0.033
Difference between 6-m routine DBP and first trimester DBP	279	−0.3	8.7	73	0.8	7.4	0.291

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; eGFR indicates estimated glomerular filtration rate; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; SBP, systolic blood pressure. ALP, Alkaline Phosphatase; GGT, Gamma glutamyl transpeptidase; ALT, Alanine transaminase; and AST, aspartate aminotransferase.

Women who had preeclampsia with elevated sphygmomanometry BP at 6 months had similar values for all other cardiovascular risk factors as women who had preeclampsia with ongoing normal BP at 6 months (Table S3).

DISCUSSION

This study highlights 4 key findings: (1) young women who have had a normotensive pregnancy 6 months ago have upper limits of BP that are lower than that usually recommended to define hypertension. Accordingly, high BP is found more often postpartum in women who have had preeclampsia if it is defined by these new limits rather than those traditionally recommended; (2) Use of 24-hour ABPM, the gold standard for diagnosing hypertension, detects hypertension more often in women who have had preeclampsia than accurate sphygmomanometric BP measurement; (3) Six months after pregnancy women who have had preeclampsia have more insulin resistance, higher BP, and more features of metabolic syndrome than women who had normotensive pregnancies; as they had greater BMI and higher BP at the start of their pregnancy it is likely that these observations 6 months postpartum reflect abnormalities brought into their pregnancy rather than having developed as a consequence of their pregnancy; (4) Our data suggest that women who have had preeclampsia have a high frequency of features consistent with EVA. All these findings have direct relevance to the postpartum investigation and management of women who have had preeclampsia and should help shape efforts to prevent long-term cardiovascular risk.

Table 3. Echocardiographic Findings 6 Months Postpartum in Women Who Had Preeclampsia or Normotensive Pregnancies

	Normotensive			Preeclampsia			
	n	Mean	SD	n	Mean	SD	*P* Value
Age, y	74	33	4.0	44	31	4.7	0.010
Height, cm	74	166	7.2	44	164	6.2	0.204
Weight, kg	74	69	14.2	44	79	18.8	0.003
BSA, m^2	74	1.7	0.2	44	1.9	0.2	0.004
LVIDD, mm	74	46.0	3.1	44	46.3	4.1	0.693
IVS, mm	74	7.9	1.0	44	8.7	1.2	<0.001
PW, mm	74	7.5	1.0	44	8.4	1.1	<0.001
Relative wall thickness	74	0.3	0.0	44	0.4	0.1	0.001
LV mass, g	74	88.4	24.6	44	109.0	29.0	<0.001
LV mass indexed, g/m2	74	50.6	12.3	44	58.8	12.6	0.001
Mitral E/A ratio	74	1.6	0.4	44	1.4	0.3	0.005
E/E′ ratio septal	74	7.51	1.4	44	8.94	2.3	<0.001
E/E′ ratio lateral	74	5.44	1.0	44	6.33	1.6	0.001
RV free-wall annulus, S'm/s	74	0.12	0.0	44	0.13	0.0	0.028
TAPSE	74	21.6	2.3	44	22.2	3.0	0.235
EF, %	74	64.6	4.0	44	63.7	3.9	0.244
GLS	74	–21.6	2.0	44	–20.7	1.9	0.022

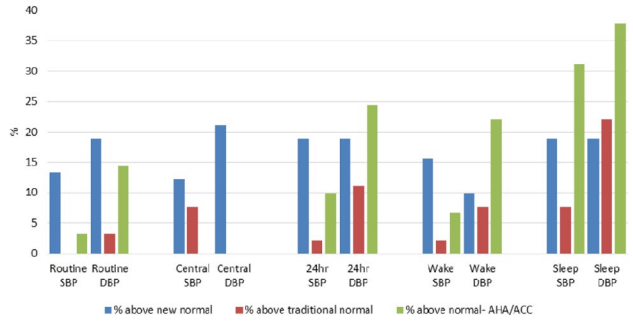
BSA indicates body surface area; EF, ejection fraction; GLS, global longitudinal strain; IVS, interventricular septum; LA, left atrial; LV, left ventricular; LVIDD, left ventricular internal dimension diastole; PW, posterior wall; RV, right ventricular; TAPSE, tricuspid annular planar systolic excursion; and TDI, tissue Doppler imaging.

The heightened long-term cardiovascular and mortality risk of women with preeclampsia has been recognized for some time now[25] and appears to be a universal phenomenon[26] that has been confirmed in more recent studies.[1,8,9] It is known that the highest cause of death in women is cardiovascular disease and that at all age groups their frequency of hypertension is close to or even greater than that of men.[27] Although women overall are more aware of a diagnosis of hypertension, this appears to often go undetected in postpartum follow-up.[28] A compounding factor is knowing what upper level of BP a caregiver should ascribe to young women after pregnancy, as this issue has not been studied specifically to date.

In 300 women who had normotensive pregnancies we found an upper limit of normal BP at 122/79 mm Hg for routine BP, similar to that defined by 24-hour ABPM in this cohort, and closer to recommended levels for defining hypertension by the American College of Cardiology/American Heart Association[17] than by the European Society of Cardiology/European Society of Hypertension committee.[16] When using these values as cut-off for defining high BP rather than general population norms we detected 13% to 19% of women who previously had preeclampsia as having high BP. The clinical implication is that to detect high BP 6 months after pregnancy this new threshold level of BP should be used. It is unknown whether this subgroup of women who had preeclampsia with postpartum elevated BP are those women who will develop a cardiovascular event but it seems logical that this subgroup carries increased vascular risk and might respond better to encouragement of the need for non-pharmacological therapies than women who had preeclampsia who have normal BP postpartum.

In addition to BP, BMI, insulin, HOMA score, triglycerides, and high-density lipoprotein cholesterol all differed significantly between women with normotensive pregnancy and women with preeclampsia at 6 months postpartum, similar to what we had observed previously in a smaller study at variable and later stages postpartum.[29] Controversy continues as to whether the cardiovascular risk of preeclampsia is independent of standard vascular risk factors or preexisting diabetes mellitus[30] or is affected by ongoing hyperlipidemia, chronic hypertension, and type 2 diabetes mellitus.[4] Unfortunately, adding a history of preeclampsia to standard risk assessment tools does not appear to improve sensitivity for cardiovascular risk detection.[31] However, our data confirm that women who have had preeclampsia have a greater propensity for metabolic syndrome 6 months postpartum than women who had a normotensive pregnancy.

It is likely that weight reduction, healthy diet, and exercise will improve long-term outcomes[32–35] but anecdotally it can be difficult to engage women in non-drug



	New normal		Traditional Normal		AHA/ACC
Routine SBP	122		140		130
Routine DBP	79		90		80
Central SBP	115		120		
Central DBP	81				
24hr SBP	121		130		125
24hr DBP	78		80		75
Wake SBP	126		135		130
Wake DBP	82		85.0		80.0
Sleep SBP	114		120.0		110.0
Sleep DBP	71		70.0		65.0

	% above new normal		% above traditional normal	P value		% above normal- AHA/ACC	P value
Routine SBP	13.3		0	< 0.001		3.3	0.015
Routine DBP	18.9		3.3	0.001		14.4	0.424
Central SBP	12.2		7.8	0.320			
Central DBP	21.1						
24hr SBP	18.9		2.2	0.035		10	0.090
24hr DBP	18.9		11.1	0.144		24.4	0.366
Awake SBP	15.6		2.2	0.002		6.7	0.058
Awake DBP	10.0		7.8	0.600		22.2	0.026
Sleep SBP	18.9		7.8	0.028		31.1	0.058
Sleep DBP	18.9		22.2	0.580		37.8	0.005

Figure 2. Percentage of women who have had preeclampsia with blood pressures above the normal ranges according to our new data (blue), traditional cut-offs (red), and American College of Cardiology/American Heart Association definitions (green). Significant difference in frequencies are indicated by *P* values of comparisons with percentage above new normal. All blood pressures are expressed as mm Hg. ACC/AHA indicates American College of Cardiology/American Heart Association; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.

therapies postpartum. Indeed, in this study the subgroup with ongoing elevated BP postpartum did not have a higher frequency of other vascular risk factors than those who have had preeclampsia with normal BP 6 months postpartum, making it hard to emphasize the cardiovascular risk. Perhaps by defining a subgroup of women with preeclampsia with demonstrably high BP postpartum we can help at least this subgroup engage more readily in lifestyle changes.

The BP at 10 weeks of gestation is a surrogate marker for pre-pregnancy BP, which was not available in this study. A new observation in this study was that BP fell slightly by 6 months postpartum from that measured by the primary care physician in early pregnancy within women with normotensive pregnancy (–4/0 mm Hg) but not in women with preeclampsia (–1/1 mm Hg; Table 2). This implies that the higher BP observed postpartum in women with preeclampsia was because of the elevated BP they brought with them into the pregnancy, rather than a specific consequence of the pregnancy.

It is generally agreed that 24-hour ABPM provides the best way of detecting true hypertension that portends the greatest cardiovascular risk.[36,37] We found that high BP was more likely to be detected using ABPM than routine sphygmomanometry (Figure 2) and would therefore recommend that this be incorporated in the assessment of women with preeclampsia 6 months postpartum wherever possible.

Our study confirms the findings of others[38] that women who had preeclampsia have greater left ventricular mass and indices suggestive of mild diastolic dysfunction postpartum but we do not have pre-pregnancy data to know whether these women entered their pregnancy with these abnormalities, a possibility given that women with preeclampsia women had elevated BP at the start of pregnancy compared with women with normotensive pregnancy.

It is known that cardiovascular disease occurs fairly soon after preeclamptic pregnancies, more commonly in the first decade or so than later,[1,30] which may represent EVA in these women, but this has been little studied to date. A key feature of EVA is increased arterial stiffness due predominantly to changes in medial wall function and structure, identified amongst other factors by elevated pulse pressure and increased central systolic and pulse pressure[39] and commonly associated with elevated HOMA score, triglycerides, and lower high-density lipoprotein cholesterol.[40]

We observed all of these features in our cohort of women with preeclampsia 6 months postpartum, supporting the notion that this group represents a cohort with EVA, either genetically or environmentally determined.

Strengths and Limitations

Strengths include the concise and consistent criteria for diagnosing preeclampsia, the prospective nature of the study with detailed analyses of BP by several methods including the gold standard of ABPM, the development of new limits of normal for these parameters based upon an appropriately aged and parous cohort, and the capacity to analyze individual changes in BP from 10 weeks of gestation to 6 months postpartum. Weaknesses include the likelihood that "sleep" BPs were overestimated as, although we recorded sleep BP from a patient diary, it is still likely that sleep was disturbed often in a cohort of women with young babies. Secondly, we have defined the upper limit of normal BPs according to the 95% confidence limits; ideally a discriminant level would be that which defined a higher versus lower risk of actual clinical cardiovascular outcomes but this will not be known in this group for many years. Thirdly, we do not yet know whether these findings will be persistent later after pregnancy, though we are studying this.[19] Finally, although we are following up with these women[19] we do not know whether the subgroup of women with preeclampsia we have identified as having elevated BP using newly defined cut-off levels or those exhibiting features of EVA at 6 months postpartum will be those women who develop the cardiovascular events, as this too will require at least a 10-year follow-up.

CONCLUSIONS

The main new clinical finding in this prospective study is the definition of new upper levels of sphygmomanometry, ambulatory, and central BPs in young women who have had a pregnancy 6 months ago. Using these levels diagnoses up to 1 in 5 women who have had preeclampsia as having ongoing elevated BP, a much greater frequency than if using traditional values to define hypertension. Only time will tell whether this subgroup are those who develop a vascular event and this will require ongoing research. In the meantime it seems prudent to advise these women in particular that they may be at higher cardiovascular risk than other women with preeclampsia and should focus even more diligently upon modifiable vascular risk factors.[34] At a minimum this might help engage such women in cardiovascular disease prevention.

PERSPECTIVES

Women with preeclampsia exhibit features of metabolic syndrome and possibly EVA 6 months postpartum. Clinicians wishing to detect high BP in these women should be aware of the lower than usual upper limit of normal for this young cohort and where possible should use 24-hour ABPM to detect these changes. Although we did not incorporate home BP in this study, it is likely that this would be a useful alternative when ABPM is not available. Future research will elucidate whether targeted BP lowering therapy is successful in preventing cardiovascular disease in this subgroup of women who have had preeclampsia.

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Disclosures

None.

Supplementary Material

Tables S1–S3

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Supplemental Material

Table S1. Characteristics of study participants and non-participants. 'Booking' is the gestation at 1st presentation to the primary care physician or hospital clinic. GP = general practitioner/primary care physician; BMI = body mass index; SBP = systolic BP; DBP = diastolic BP.

	Normotensive Pregnancies						
	Participants			Non participants			
	n	Mean	SD	n	Mean	SD	p-value
BMI- at booking	302	24	5	2451	24	5	0.150
Gestation Booking BP (weeks)	281	10	5	2449	14	7	<0.001
Booking GP SBP (mmHg)	281	108	11	2222	101	11	<0.001
Booking GP DBP (mmHg)	281	67	8	2222	62	7	<0.001
Gestation at Birth (weeks)	302	39	2	2452	39	2	0.100
Age at First assessment (yrs.)	302	33	5	2452	31	5	<0.001
Apgar 1	300	9	1	2438	9	1	0.069
Apgar 5	300	9	1	2439	9	1	0.827

	Pre-Eclampsia						
	Participants			Non participants			
	n	Mean	SD	n	Mean	SD	p-value
BMI- at booking	90	26	5	55	27	6	0.230
Gestation Booking BP (weeks)	73	10	5	55	12	8	0.046
Booking GP SBP (mmHg)	74	113	12	52	110	11	0.161
Booking GP DBP (mmHg)	74	71	8	52	69	8	0.304
Gestation at Birth (weeks)	90	37	3	55	38	2	0.326
Age at First assessment (yrs.)	90	32	5	55	31	5	0.679
Apgar 1	90	8	2	55	8	2	0.019
Apgar 5	90	9	1	55	9	1	0.136

	Normotensive Pregnancies (%)			Pre-Eclampsia (%)		
	Participants (n=302)	Non participants (n=2452)	p-value	Participants (n=90)	Non participants (n=55)	p-value
Labour Onset - Spontaneous	58	45	<0.001	9	9	0.175
Induced	32	40		66	78	
No Labour	10	14		26	13	
Vaginal Birth	81	71	<0.001	51	64	0.141
MgSO4 given	0	0.1	0.015	24.4	3.6	0.001
Baby Gender- Male	51	52	0.661	48	49	0.878

Table S2. Frequency of high blood pressure at six months postpartum detected by various methods, using only awake ABPM as the gold standard method for diagnosing high BP.

		Above SBP Routine sphygmomanometry using new normal range	Above SBP Routine sphygmomanometry using traditional definitions	Above SBP Routine sphygmomanometry using AHA/ACC definitions	Above SBP Central using new normal range	Above SBP Central using traditional values
Above awake SBP	No	9	0	2	8	6
	Yes	3	0	1	3	1
Total		12	0	3	11	7

		Above DBP Routine sphygmomanometry using new normal range	Above DBP Routine sphygmomanometry using traditional definitions	Above DBP Routine sphygmomanometry using AHA/ACC definitions	Above DBP Central using new normal range
Above awake DBP	No	12	2	6	15
	Yes	5	1	7	4
Total		17	3	13	19

Table S3. Parameters for formerly pre-eclamptic women with high blood pressure defined by the new normal range vs. formerly pre-eclamptic women with blood pressure in the normal range at 6 months post-partum.

	Pre-eclampsia with Routine BP above New Normal			Pre-eclampsia with normal BP 6 months post-partum			
	n	Mean	SD	n	Mean	SD	p-value
BMI	11	30.1	7.4	79	27.5	5.6	0.276
Creatinine (mg/dL)	11	0.7	0.1	78	0.7	0.1	0.494
eGFR (mL/min)	11	96.2	8.5	78	96.8	7.6	0.821
ALP (IU)	10	80.3	16.7	77	83.7	21.1	0.572
GGT (IU)	10	29.4	22.9	77	18.8	24.4	0.198
ALT (U/L)	10	22.5	12.9	77	20.9	11.3	0.717
AST (U/L)	10	21.7	6.2	75	20.8	5.7	0.662
Glucose (mg/dL)	11	86.4	8.2	78	85.7	6.9	0.802
Urate (mg/dL)	11	5.39	0.84	77	4.86	1.07	0.076
White cell count (10^9/L)	11	6.0	1.5	78	5.8	1.9	0.706
Hb (g/dL)	11	13.1	1.2	78	13.0	0.9	0.698
Platelets (10^9/L)	11	264.6	45.5	77	259.4	61.0	0.735
Cholesterol (mg/dL)	11	185.3	21.3	77	179.8	35.6	0.476
LDL (mg/dL)	11	112.3	23.9	77	104.6	31.5	0.355
HDL (mg/dL)	11	56.2	17.9	78	59.8	14.3	0.525
Triglyceride (mg/dL)	11	86.2	68.2	77	76.1	48.4	0.647
Aldosterone (ng/dL)	10	11.7	8.8	77	10.7	9.6	0.746
Renin (mU/L)	9	10.6	8.7	75	16.9	11.1	0.071
Aldosterone:Renin ratio	9	105.1	218.3	75	24.5	23.6	0.300
Insulin (mU/L)	11	12.3	9.4	77	9.2	8.1	0.308
HBA1C (%)	11	5.2	0.2	78	5.2	0.3	0.922
Vitamin D (ng/mL)	11	27.2	7.7	77	27.3	7.4	0.995
HOMA score	11	2.7	2.0	77	2.0	1.7	0.304
Urine albumin/creat (mg/g)	11	25.8	31.1	77	18.7	27.5	0.486