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Cardiovascular Biomarkers and Blood Pressure at 6 Weeks and 6–12 Months Postpartum in Women With or Without Hypertensive Disorders During Pregnancy: A Prospective Study

Jarawee Sukmanee, M.D., Ph.D.[1], Penkae Rothmanee, M.D.[2], Wilaiwan Sriwimol, Ph.D.[3], Anne Cathrine Staff, M.D., Ph.D.[4,5], Tippawan Liabsuetrakul, M.D., Ph.D.[1,6]

[1]Department of Epidemiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
[2]Division of Obstetrics and Gynecology, Naradhiwas Rajanagarindra Hospital, Mueang Narathiwat 96000, Thailand.
[3]Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
[4]Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway.
[5]Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Norway.
[6]Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

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Abstract:

Objective: To measure and compare cardiovascular biomarkers and blood pressure in women with hypertensive disorders of pregnancy (HDP) to those with normotensive pregnancies evaluated at 6 weeks and 6–12 months after delivery.

Material and Methods: A prospective cohort study of postpartum women following HDP and normotensive pregnancies at 6 weeks and 6–12 months postpartum was conducted. Postpartum blood pressure and cardiovascular biomarkers including body mass index (BMI), levels of serum high-sensitivity C-reactive protein (hs-CRP), creatinine, glucose, glycated hemoglobin, low-density lipoprotein cholesterol, and levels of urine microalbumin/creatinine ratio (UACR), sodium, and potassium were quantified.

Results: A total of 118 women involving 40 with previous preeclampsia (PE), 27 with gestational hypertension (GHT), 10 with chronic hypertension (CHT) during recent pregnancy, and 41 normotensive pregnancies were enrolled at 6 weeks postpartum, of whom 73 (61.9%) completed the study at 6–12 months postpartum. Women in the PE and GHT groups had significantly elevated blood pressure, serum hs-CRP and hypertension at 6 weeks and 6–12 months postpartum.

Contact: Prof. Tippawan Liabsuetrakul, M.D., Ph.D.
Department of Epidemiology, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand.
E-mail: tippawan.l@psu.ac.th

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Both the PE and CHT groups had an increase in UACR at 6–12 months postpartum. Multivariate linear regression showed that a history of PE and GHT was independently and persistently associated with increased postpartum blood pressure. **Conclusion:** Women with HDP had increased blood pressure, risk of hypertension, and increased levels of biomarkers associated with cardiovascular risk at both 6 weeks and 6–12 months postpartum, including serum hs-CRP and UACR. Women with HDP should be counselled about cardiovascular risks as early as 6 weeks postpartum.

Keywords: blood pressure, cardiovascular disease, gestational hypertension, hypertension, postpartum, preeclampsia

Introduction

Hypertensive disorders in pregnancy (HDP), including pre-existing chronic hypertension and pregnancy-induced hypertension which is classified into gestational hypertension (GHT) and preeclampsia (PE), are well-known obstetric complications that contribute to increased maternal morbidity and mortality worldwide. The World Health Organization (WHO) has identified HDP as the second most common cause of maternal death, particularly in low- and middle-income countries[1]. A cohort study in Australia showed that HDP was strongly and independently associated with future hypertension after the index pregnancy, after adjusting for confounders[2]. Various large population-based studies over the last two decades[3–5] have reported increased cardiovascular risk in mothers following hypertensive disorders or other high-risk obstetric syndromes associated with placental dysfunction, as summarized by Staff et al.[6].

A recent systematic review also summarized that women with a history of PE had a higher risk of hypertension and cardiovascular diseases (CVD), dyslipidemia, abnormal renal function, type 2 diabetes mellitus, and metabolic syndromes compared to women with a previous normotensive pregnancy[7]. National data from Denmark[8], Norway[9], and France[10] also indicate a faster onset of chronic hypertension (CHT) in women with previous HDP compared to women with previous normotensive pregnancies. However, the mechanisms mediating future hypertension and CVD after HDP, especially PE, are not well understood, but may be linked to endothelial dysfunction during pregnancy and genetic-environmental risk factors[11].

The hypertensive disorders initially occurring during pregnancy usually resolve by 6–12 weeks of postpartum. If hypertension persists, particularly beyond 6 months postpartum, CHT should be considered and investigated[12]. A recent systematic review found that the risk of developing postpartum hypertension was higher in the first 6 months following delivery with HDP, with similar results for GHT and PE, but considerable heterogeneity was found[13]. A study published in 2015 found that both de novo and persistent postpartum hypertension were higher in women with hypertensive pregnancies and an elevated ratio of soluble fms-like tyrosine kinase 1 to placental growth factor (sFlt-1/PlGF) was found[14]. In contrast, a study published in 2021 found that these angiogenic factors, when measured in the third trimester, were not useful as predictors of postpartum hypertension[15].

Previous studies have highlighted traditional cardiovascular risk markers, including blood pressure, body mass index (BMI), lipid profiles, glucose intolerance, and microalbuminuria in women following a pregnancy complicated by PE syndrome[12,16]. High sensitivity C-reactive protein (hs-CRP), a systemic inflammation marker associated with increased risk of CVD, has also been studied following PE[17]. However, the biomarker findings of these postpartum studies after a history of HDP are inconsistent, reporting either no correlation or higher levels

in women with previous HDP compared to those with normotensive pregnancies[16,18], and/or that any associations were influenced by differences in maternal age and BMI[8,17]. To date, there has been no published study related to these cardiovascular biomarkers in women with HDP after delivery in Asia, including Thailand.

Although intensified follow-ups of women after a pregnancy complicated by HDP is recommended, including regular monitoring of blood pressure in a medical setting[6,19,20], such follow-up recommendations are likely mostly neglected. A study from Norway found that available cardiovascular risk scores were inadequate in assessing risk one-year postpartum following hypertensive pregnancies, and suggested further studies to improve targeting of women at cardiovascular risk[21]. The integration of potential biomarkers as well as metabolic and behavioral markers in prediction algorithms needs to be explored. This study aimed to measure and compare cardiovascular biomarkers and blood pressure in women with hypertensive disorders of pregnancy (HDP) to those with normotensive pregnancies evaluated at 6 weeks and 6-12 months after delivery.

Material and Methods

Study design and setting

A prospective cohort study was conducted in the southern region of Thailand, where HDP is common[22]. Songkhla and Narathiwat provinces were selected as the specific provinces, providing a representative sampling of the different religious and social population characteristics of southern Thailand. From each province, a tertiary hospital having approximately 4,000 deliveries each year was selected as the study hospital.

Study participants

All singleton pregnant Thai women aged 18 years or more who gave birth in the two study hospitals from October 1, 2019, to August 31, 2021, were screened for eligibility. The eligibility criteria were women diagnosed with HDP during their most recent pregnancy and normotensive women who matched on age and parity to those with HDP as a comparison group. Those who were non-Thai citizens or had communication barriers such as deafness or mental deficit were excluded. At least 24 women with HDP and 24 normotensive pregnancies were required based on the sample size calculation using mean differences of urine microalbumin/creatinine ratio at 6 weeks postpartum between women with HDP and normotensive pregnancies. After the lists of eligible women were retrieved from the computerized Hospital Information System, the postpartum women were contacted by phone and invited to participate in the study. All enrolled women provided written informed consent at their first study visit 6 weeks following the birth of their most recent baby. The study was approved by the Institute Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC. 62-135-18-1), and approval to conduct the study was obtained from the hospitals' directors.

Exposure assessment

The exposed group included women diagnosed as HDP during the most recent pregnancy that consisted of GHT, PE, and Chronic hypertension (CHT), as classified based on the International Society of Study of Hypertension in Pregnancy (ISSHP) recommendations[23]. The GHT was defined as new-onset hypertension (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg) after 20 weeks of gestation. The PE was defined as new-onset hypertension plus proteinuria, which was defined as ≥300 mg/24 hours, a protein to creatinine ratio ≥0.3, or a urine dipstick reading of 2+ (in the absence of urinary tract infection). The CHT was defined as hypertension that developed before 20 weeks of gestation, including prior to pregnancy. Unexposed group were women with normotensive pregnancies without CHT and without any diagnosis of HDP during their most recent pregnancy.

Data collection

Eligible women who agreed to participate were invited to attend two postpartum study visits, at 6 weeks and at 6–12 months after delivery, including collection of blood and urine samples during a morning visit after fasting overnight for 12 hours. A trained research assistant interviewed the participating women for demographic, obstetric, and behavioral information at the first study visit. Body weight, height, and blood pressure were also measured at each visit by a research assistant, as detailed below. Morning spot urine and fasting blood samples were then collected from the participating women

Physical activity was assessed using the Thai version of the Global Physical Activity Questionnaire (GPAQ)[24]. The metabolic equivalent of task (MET)-minutes of total physical activity per week was calculated. At least ≥600 MET-minutes per week, as recommended by the WHO for healthy physical activity, was used to dichotomize for sufficient or insufficient physical activity. Sleep quality was evaluated using the Thai version of the Pittsburgh Sleep Quality Index (PSQI)[25]. The PSQI is based on sleep scores of seven domains ranging from 0 to 21, of which an overall score >5 indicates poor sleep quality[26].

Body weight was measured after all heavy clothing was removed. Body mass index (BMI) was calculated from weight in kilograms divided by the square of the height in meters[27]. SBP and DBP were measured in mmHg after the woman had rested for at least 15 minutes, using an automatic cuff-oscillometric device, validated for pregnancy (MIT Elite HEM-7300; Omron Healthcare, Kyoto, Japan)[28]. The average of three consecutive blood pressure measurements was used. Current hypertension was defined as SBP measured at study visit ≥140 mmHg and/or DBP ≥90 mmHg, or a current antihypertensive treatment (where the woman was diagnosed with chronic hypertension previously). Prehypertension was defined as blood pressure 120–139/80–89 mmHg[29].

Laboratory methods

The biomarkers measured in this study were serum hs-CRP assessed by a particle enhanced immunoturbidimetric method, urine and serum creatinine assessed by enzymatic colorimetric method, fasting blood glucose (FBS) assessed by enzymatic hexokinase method, glycated hemoglobin (HbA1c) assessed by a capillary electrophoresis method, low-density lipoprotein (LDL) and cholesterol assessed by a homogeneous enzymatic colorimetric method, urine microalbumin/creatinine ratio (UACR) of which the urine microalbumin was measured by an immunoturbidimetric method, and urine sodium and potassium measured using the indirect ion-selective electrodes method. The biomarkers were measured using a Cobas 6000 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany), except for HbA1c, which was measured using a Capillarys 3 Tera (Sebia, France) machine at the clinical chemistry laboratory of our institution (Songklanagarind Hospital, Prince of Songkla University, Thailand).

Statistical analysis

The demographic and obstetrics information of the participants are presented descriptively. Differences in demographic and obstetrics information, physical and behavioral measures, and biomarkers among HDP or normotensive pregnancies were compared. An analysis of variance (ANOVA) or Kruskal–Wallis test was used to compare continuous variables, as appropriate. Categorical variables were compared using the chi-square or Fisher exact test. Comparisons of physical and behavioral measurements and biomarkers between the two study visits were done using the paired t-test or Wilcoxon Signed Rank test, as appropriate. Multivariate linear regression was performed using the stepwise forward selection method to assess factors associated with blood pressure at 6 weeks and 6–12 months postpartum, of which only the subset

of women without CHT was included. A model with log transformation of skewed variables was compared with a model without transformation, and the model with the better fit was selected. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted with the R program version 4.1.2[30].

Results

A total of 118 women were eligible and participated in the study at 6 weeks postpartum (PE, n=40; GHT, n= 27; CHT, n=10, and normotensive women, n=41). Only 73 women participated in the second study visit at 6–12 months postpartum (61.9%), including 23 women in the PE group (57.5%), 14 women in the GHT group (51.8%), 8 women in the CHT group (80.0%), and 28 women in the normotensive group (68.3%), as shown in Figure 1.

The demographic and obstetric information of the 118 included women at enrollment is presented per study group in Table 1. The mean ages of the participating women were the lowest, 32.1 years, in normotensive group and highest, 36.7 years, in CHT group. Of the 40 women in the PE group, 6 women had developed superimposed PE. We identified some differences in the distribution of religions, with slightly higher rates of Islam in the PE and CHT groups. More than half of the women in the GHT group were Buddhists. Women in the PE and CHT groups were more likely to have a history of HDP in the family than women in the GHT and normotensive groups. The majority of women in the CHT group had an education off less than a bachelor's degree. The highest rates of obesity and gestational diabetes were observed in the CHT group (90% and 60%, respectively). Preterm birth and low infant birth weight were most prevalent in the PE group (39% and 41%, respectively). We found no significant differences in rates of family history of hypertension and cardiovascular disease between the groups. Most SGA babies were in the PE group (7 of 9).

Figure 2 shows the individual levels of blood pressure at 6 weeks and 6–12 months postpartum by delivery outcome groups (Figure 2A, SBP; Figure 2B, DBP). Women in the CHT group had the highest levels of systolic and diastolic blood pressure at both study visits, followed by women in the PE and GHT groups. Compared to the 6-week postpartum study visit, a decline in blood pressure at 6–12 months was found in all groups except for the CHT group. Two women in the PE group and one woman in the normotensive group were classified as having hypertension at 6 weeks but were normotensive at the 6–12 months postpartum study visit.

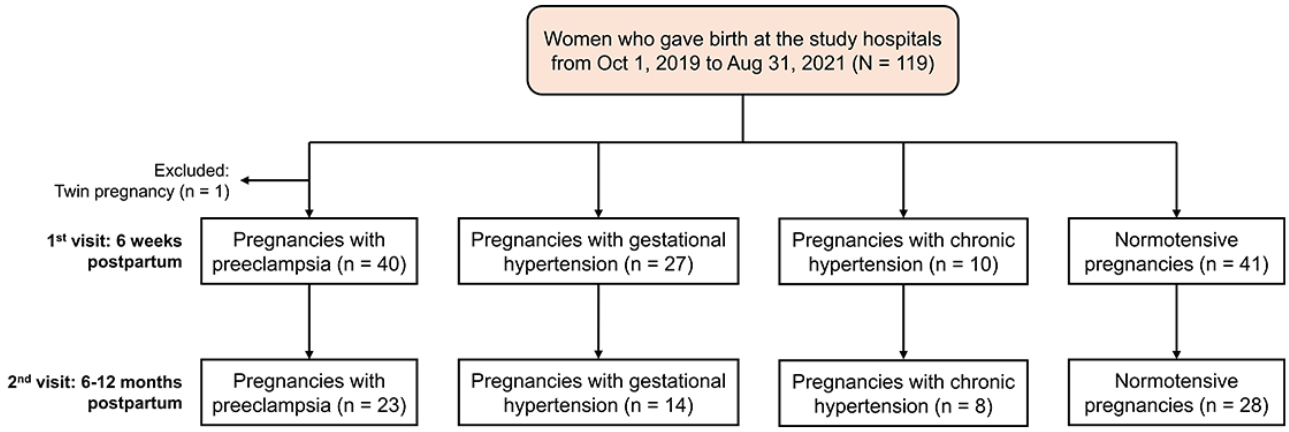

Figure 1 Study flowchart

Table 1 Demographic and obstetrics information of postpartum women at enrollment, by exposure index pregnancy group (N=118)

Characteristic	PE (n=40)	GHT (n=27)	CHT (n=10)	Normotensive (n=41)	p-value
Age (years), mean (S.D.)	32.4 (5.4)	32.8 (4.0)	36.7 (4.7)	32.1 (4.3)	0.045†
Religion					0.012‡
Buddhism	18 (45.0)	21 (77.8)	4 (40.0)	19 (46.3)	
Islam	22 (55.0)	5 (18.5)	6 (60.0)	22 (53.7)	
Christian	0 (0.0)	1 (3.7)	0 (0.0)	0 (0.0)	
Education					<0.001‡
Less than bachelor's degree	15 (37.5)	2 (7.4)	7 (70.0)	9 (22.0)	
Bachelor's degree or higher	25 (62.5)	25 (92.6)	3 (30.0)	32 (78.0)	
Underlying disease					
Chronic hypertension	6 (15.0)	0 (0.0)	10 (100.0)	0 (0.0)	<0.001‡
Diabetes mellitus	0 (0.0)	1 (3.7)	1 (10.0)	0 (0.0)	0.056‡
Dyslipidemia	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0.649‡
Family history					
Family history of hypertension	23 (57.5)	10 (37.0)	7 (70.0)	15 (36.6)	0.080‡
Family history of cardiovascular disease	6 (15.0)	4 (14.8)	1 (10.0)	4 (9.8)	0.914‡
Family history of HDP	8 (20.0)	1 (3.7)	2 (20.0)	1 (2.4)	0.022‡
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.2 (21.6, 28.3)	25.2 (22.9, 29.4)	28.0 (26.6, 32.0)	21.4 (19.5, 24.1)	<0.001†
Characteristics of most recent pregnancy					
Nulliparity	17 (42.5)	20 (74.1)	3 (30.0)	19 (46.3)	0.030‡
Gestational diabetes	8 (20.0)	7 (25.9)	6 (60.0)	2 (4.9)	<0.001‡
Preterm birth (<37 weeks of gestation)	15 (37.5)	3 (11.1)	2 (20.0)	2 (4.9)	0.001‡
Low birth weight infant (<2,500 g)	16 (40.0)	1 (3.7)	2 (20.0)	2 (4.9)	<0.001‡
SGA infant (<10th birth weight centile)	7 (17.5)	1 (3.7)	0 (0.0)	1 (2.4)	0.065‡

Data are reported as n (%) unless stated otherwise, †Kruskal–Wallis test, ‡Chi-square or Fisher exact test
BMI=body mass index, CHT=chronic hypertension, GHT=gestational hypertension, HDP=hypertensive disorder in pregnancy, PE=preeclampsia, SGA=small for gestational age, S.D.=standard deviaion, IQR=interquartile range

Levels of physical and behavioral measurements at the 6 weeks and 6–12 months postpartum study visits by exposure groups are presented in Table 2. The prevalence of de novo hypertension at both postpartum study visits was highest in the PE group (33.3% and 23.8%), followed by the GHT group (21.4% and 21.4%). The proportions of women with prehypertension showed non-significant differences, but with higher in PE, thereafter GHT and with the lowest rate in the normotensive group. Women in the CHT group tended to have higher BMIs, while normotensive women tended to lactate longer than the other groups. The percentages of women reporting insufficient physical activity and poor sleep quality were not different between the groups. Apart from a significant decrease in the proportion of women with poor sleep quality in the PE group, we found non-significant changes in physical and behavioral measurements at 6–12 months compared to those at 6 weeks postpartum.

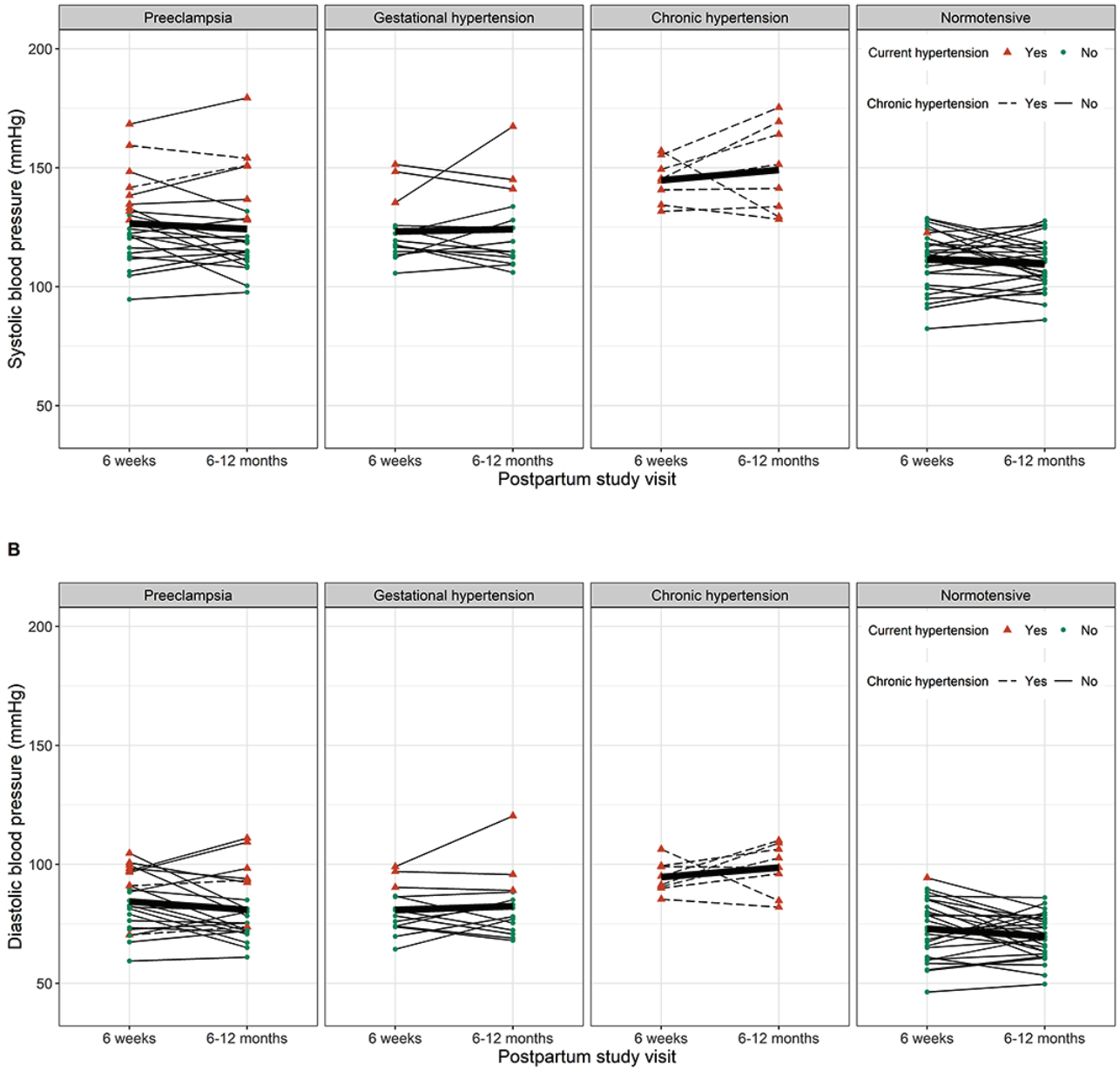

Figure 2 Levels of systolic blood pressure (A) and diastolic blood pressure (B) per woman with previous preeclampsia, gestational hypertension, chronic hypertension, and normotensive pregnancies at the 6 weeks and 6–12 months postpartum study visits

Table 2 Levels of physical and behavioral measurements at 6 weeks and 6–12 months postpartum study visits, by index pregnancy group (N=73)

Measure	PE (n=23)	GHT (n=14)	CHT (n=8)	Normotensive (n=28)	p-value
6 weeks postpartum					
Postpartum duration (months), median (IQR)	1.7 (1.4,2.0)	1.6 (1.5,1.7)	1.6 (1.5,1.7)	1.5 (1.4,1.7)	0.496†
Systolic blood pressure (mmHg), mean (S.D.)	126.2 (17.3)	123.2 (13.3)	144.8 (9.1)	111.4 (12.3)	<0.001§
Diastolic blood pressure (mmHg), mean (S.D.)	83.9 (12.4)	80.8 (10.1)	94.6 (6.7)	72.9 (12.3)	<0.001§
Current hypertension (≥140/90 mmHg, self-reported, treated)	9 (39.1)	3 (21.4)	8 (100.0)	1 (3.6)	<0.001‡
Current prehypertension (120–139/80–89 mmHg)	12 (52.2)	6 (42.9)	–	10 (35.7)	0.528‡
Postpartum BMI (kg/m^2), mean (S.D.)	25.5 (4.5)	26.1 (3.6)	29.3 (5.4)	24.4 (5.1)	0.073§
Lactation duration (months), median (IQR)	1.6 (1.4, 1.9)	1.6 (1.4, 1.6)	1.6 (1.3, 1.6)	1.5 (1.4, 1.7)	0.461†
Insufficient physical activity	18 (78.3)	13 (92.9)	8 (100.0)	24 (85.7)	0.498‡
Poor sleep quality (PSQI global score >5)	22 (95.7)	12 (85.7)	6 (75.0)	25 (89.3)	0.356‡
6–12 months postpartum					
Postpartum duration (months), median (IQR)	7.8 (7.0, 10.4)	7.7 (7.3, 10.4)	10.3 (7.8, 11.9)	7.8 (6.8, 11.4)	0.615†
Systolic blood pressure (mmHg), mean (S.D.)	124.1 (19.3)	124.2 (17.4)	149.1 (18.7)	109.4 (10.4)	<0.001§
Diastolic blood pressure (mmHg), mean (S.D.)	80.7 (13.3)	82.4 (13.7)	98.7 (10.6)	69.7 (9.2)	<0.001§
Current hypertension (≥140/90 mmHg, self-reported, treated)	7 (30.4)	3 (21.4)	8 (100.0)	0 (0.0)	<0.001‡
Current prehypertension (120–139/80–89 mmHg)	8 (34.8)	5 (35.7)	–	4 (14.3)	0.157‡
Postpartum BMI (kg/m^2), mean (S.D.)	25.6 (5.3)	26.1 (3.9)	29.6 (4.6)	24.3 (5.3)	0.072§
Lactation duration (months), median (IQR)	6.6 (3.0, 7.9)	5.5 (3.0, 6.9)	5.9 (2.4, 7.9)	7.2 (6.1, 9.1)	0.083†
Insufficient physical activity	13 (56.5)	13 (92.9)	6 (75.0)	18 (64.3)	0.105‡
Poor sleep quality (PSQI global score >5)	16 (69.6)	8 (57.1)	5 (62.5)	21 (75.0)	0.646‡

Data are reported as n (%) unless stated otherwise, †Kruskal–Wallis test, ‡Chi-square or Fisher exact test, §Analysis of variance (ANOVA)
BMI=body mass index, CHT=hypertension, GHT=gestational hypertension, HDP=hypertensive disorder in pregnancy, MET=metabolic equivalent of task, PE=preeclampsia, PSQI=Pittsburgh Sleep Quality Index, S.D.=standard deviaion, IQR=interquartile range

The levels of biomarkers at the 6 weeks and 6–12 months postpartum study visits by exposure groups are shown in Table 3. The median serum FBS and HbA1c levels at the 6–12 months postpartum study visit were highest in the CHT group. More women in the CHT group had a serum FBS ≥126 mg/dL and HbA1c ≥6.5% at 6–12 months postpartum than the other groups (Table 3). Women in the PE and GHT groups were more likely to have higher serum hs-CRP at both study visits than the other groups. The median UACR at the 6–12 months postpartum study visit was highest in the CHT group, followed by the PE group. Levels of serum creatinine, urine sodium, and urine potassium, and the urine sodium/potassium ratio at the 6 weeks and 6–12 months postpartum study visits, were similar across all groups. Compared to 6 weeks postpartum, the levels of serum LDL cholesterol in the normotensive group and serum creatinine in the PE and GHT groups at 6–12 months were significantly lower. In the PE group, serum hs-CRP decreased and urine sodium increased at the 6–12 months postpartum study visit compared to 6 weeks. The urine potassium/creatinine ratios significantly increased at the second visit in all groups except for the CHT group. The urine potassium levels increased only in the GHT group.

The final models of multivariate analyses to identify factors associated with blood pressure at 6 weeks and 6–12 months postpartum study visits are shown in Table 4. After adjustment for various measurements and biomarkers,

GHT was consistently associated with high systolic and diastolic blood pressures at both postpartum study visits when compared to normotensive pregnancies. A similar pattern was observed following PE, except there was no significant association between a history of PE and SBP at 6–12 months postpartum. Pre-pregnancy BMI, not postpartum BMI, was positively associated with systolic and diastolic blood pressures at 6 weeks postpartum, while a family history of HDP and lactation duration were positively associated with both markers at 6–12 months postpartum.

Table 3 Levels of biomarkers at 6 weeks and 6–12 months postpartum study visits, by index pregnancy group (N=73)

Biomarker	PE (n=23)	GHT (n=14)	CHT (n=8)	Normotensive (n=28)	p-value
6 weeks postpartum					
Serum FBS (mg/dL), median (IQR)	81.9 (80.0, 86.0)	82.4 (80.0, 87.9)	84.9 (77.3, 99.8)	81.2 (77.2, 86.5)	0.818†
Serum FBS categories (≥126 mg/dL)	1 (4.3)	1 (7.1)	0 (0.0)	0 (0.0)	0.462‡
Serum HbA1c (%), median (IQR)	5.3 (5.1, 5.6)	5.2 (5.1,5.5)	5.6 (5.3, 5.7)	5.2 (5.1, 5.4)	0.447†
Serum HbA1c categories (≥6.5%)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	0.301‡
Serum LDL cholesterol (mg/dL), mean (S.D.)	137.2 (31.4)	167.3 (45.1)	151.3 (41.2)	136.6 (39.4)	0.075§
Serum LDL cholesterol categories (≥130 mg/dL)	12 (52.2)	11 (78.6)	5 (62.5)	15 (53.6)	0.409‡
Serum creatinine (mg/dL), mean (S.D.)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.414§
Serum hs-CRP (mg/L), median (IQR)	3.6 (1.9, 5.0)	3.2 (2.3, 4.9)	1.9 (0.9, 3)	1.2 (0.9, 3.2)	0.035†
UACR (mg/g Cr), median (IQR)	18.5 (7.0, 56.7)	8.7 (3.9, 16.3)	8.1 (4.5, 23.6)	7.9 (6.5, 10.4)	0.217†
Urine sodium (mmol/L), mean (S.D.)	117.9 (43.3)	157.7 (53.6)	145.8 (47.8)	147.2 (57.9)	0.101§
Urine sodium/creatinine ratio, mean (S.D.)	14.5 (10.8)	19.1 (7.5)	15.3 (8.1)	14.1 (7.6)	0.349§
Urine potassium (mmol/L), mean (S.D.)	43.4 (19.1)	44.7 (18.3)	44 (19.9)	52.1 (28.3)	0.540§
Urine potassium/creatinine ratio, median (IQR)	4.0 (2.3, 5.6)	4.5 (3.9,6.6)	2.9 (2.6, 4.9)	4.6 (3, 5.6)	0.636†
Urine sodium/potassium ratio, median (IQR)	3.0 (1.7, 4.1)	3.2 (2.9, 4.2)	3.2 (2.9, 4.0)	3.3 (1.8, 4.4)	0.749†
6–12 months postpartum					
Serum FBS (mg/dL), median (IQR)	86.0 (80.9, 88.6)	82.3 (77.2, 89.5)	94.0 (88.9, 128.0)	81.2 (75.8, 86.4)	0.015†
Serum FBS categories (≥126 mg/dL)	1 (4.3)	2 (14.3)	2 (25.0)	0 (0.0)	0.022‡
Serum HbA1c (%), median (IQR)	5.5 (5.2, 5.8)	5.4 (5.3, 5.7)	6.1 (5.2, 7.1)	5.2 (5, 5.4)	0.020†
Serum HbA1c categories (≥6.5%)	3 (13.0)	2 (14.3)	3 (37.5)	0 (0)	0.011‡
Serum LDL cholesterol (mg/dL), mean (SD)	127.7 (34.3)	147.6 (47.1)	128.1 (16.8)	118.9 (29.3)	0.094§
Serum LDL cholesterol categories (≥130 mg/dL)	12 (52.2)	8 (57.1)	4 (50.0)	8 (28.6)	0.209‡
Serum creatinine (mg/dL), mean (S.D.)	0.7 (0.1)	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)	0.528§
Serum hs-CRP (mg/L), median (IQR)	2.2 (0.6, 4.1)	2.6 (1.6, 5.2)	1.6 (1.2, 3.0)	0.8 (0.5, 2.3)	0.027†
UACR (mg/g Cr), median (IQR)	12.1 (6.9, 52.8)	6.3 (5.1, 23.7)	15.4 (13.0, 24.7)	6.2 (4.0, 10.6)	0.027†
Urine sodium (mmol/L), mean (S.D.)	149.8 (58.4)	160.2 (61.7)	171.7 (50.6)	148.6 (74.2)	0.800§
Urine sodium/creatinine ratio, mean (S.D.)	17.8 (9.8)	15.4 (5.8)	16.4 (7.7)	15.8 (8.3)	0.816§
Urine potassium (mmol/L), mean (S.D.)	50.9 (25.6)	72.3 (38.5)	56.6 (27.3)	64.2 (32.7)	0.209§
Urine potassium/creatinine ratio, median (IQR)	4.9 (3.8, 6.7)	6.0 (5.2, 7.9)	4.1 (3.5, 4.8)	5.2 (4.3, 7.0)	0.140†
Urine sodium/potassium ratio, median (IQR)	3.1 (2.3,4.4)	2.6 (1.5, 3.1)	3.5 (2.3, 4.5)	2.6 (1.7, 4.0)	0.435†

Data are reported as n (%) unless stated otherwise, †Kruskal–Wallis test, ‡Chi-square or Fisher exact test, §Analysis of variance (ANOVA)
CHT=chronic hypertension, Cr=creatinine, FBS=fasting blood sugar, GHT=gestational hypertension, HbA1c=glycated hemoglobin, HDP=hypertensive disorder in pregnancy, hs-CRP=high-sensitivity C-reactive protein, LDL=low-density lipoprotein, PE=preeclampsia, UACR=urine microalbumin/creatinine ratio, S.D.=standard deviaion, IQR=interquartile range

Table 4 Univariate and multivariate analyses of factors associated with blood pressure at 6 weeks (N=102) and 6–12 months (N=63) postpartum study visit

Variable	Systolic blood pressure		Diastolic blood pressure	
	β coef. (95% CI)	Adj. β coef. (95% CI)	β coef. (95% CI)	Adj. β coef. (95% CI)
6 weeks postpartum				
Pregnancy complication: ref=Normotensive				
Preeclampsia	15.9 (9.81, 21.99)	12.97 (7.39, 18.55)	13.81 (8.62, 19.00)	9.48 (4.38, 14.59)
Gestational hypertension	9.83 (3.38, 16.29)	11.23 (4.82, 17.65)	7.13 (1.62, 12.63)	6.34 (0.86, 11.81)
Age	0.70 (0.08, 1.32)	–	0.47 (–0.06, 1.00)	0.50 (0.07, 0.94)
Religion: ref=Buddhism				
Islam	4.90 (–0.94, 10.73)	5.46 (0.40, 10.51)	3.65 (–1.32, 8.62)	4.11 (–0.15, 8.37)
Christian	–0.57 (–29.92, 28.78)	–2.67 (–25.41, 20.07)	–11.69 (–36.68, 13.31)	–6.82 (–26.82, 13.18)
Family history of hypertension	6.33 (0.58, 12.08)	4.84 (0.13, 9.55)	5.00 (0.07, 9.93)	–
Pre-pregnancy BMI	1.16 (0.60, 1.73)	0.65 (0.11, 1.19)	0.88 (0.39, 1.37)	0.65 (0.21, 1.08)
Multiparity: ref=Nulliparity	7.57 (1.91, 13.22)	5.00 (–0.12, 10.12)	6.39 (1.56, 11.22)	–
Gestational diabetes	–0.93 (–9.14, 7.28)	–5.93 (–12.49, 0.62)	–1.60 (–8.60, 5.40)	–4.72 (–10.42, 0.99)
Lactation duration (months)	3.33 (–5.06, 11.72)	–	2.16 (–5.00, 9.33)	–5.24 (–11.33, 0.85)
Sedentary time (hours/day)	0.01 (–0.01, 0.04)	1.83 (0.59, 3.06)	–0.11 (–1.41, 1.19)	–
Sleep duration (hours)	–0.70 (–2.67, 1.28)	–1.31 (–2.89, 0.27)	–1.10 (–2.78, 0.57)	–1.08 (–2.44, 0.29)
Serum FBS	0.32 (0.11, 0.52)	0.24 (0.05, 0.43)	0.22 (0.04, 0.40)	–
Serum creatinine	17.78 (–6.17, 41.72)	–	22.82 (2.67, 42.97)	24.40 (7.73, 41.06)
Log (UACR)	3.71 (1.55, 5.88)	–	3.55 (1.73, 5.37)	2.80 (1.11, 4.49)
Urine potassium	–0.14 (–0.26, –0.01)	–0.10 (–0.20, 0.00) Adjusted R^2=0.45	–0.07 (–0.18, 0.04)	– Adjusted R^2=0.40
6–12 months postpartum				
Pregnancy complication: ref=Normotensive				
Preeclampsia	11.97 (3.18, 20.75)	5.5 (–1.17, 12.16)	10.97 (3.99, 17.94)	6.92 (1.45, 12.39)
Gestational hypertension	14.75 (4.93, 24.57)	10.63 (2.77, 18.49)	12.71 (4.91, 20.51)	11.03 (4.66, 17.41)
Age	0.93 (0.11, 1.76)	0.17 (–0.52, 0.86)	0.81 (0.15, 1.48)	0.44 (–0.14, 1.01)
Family history of HDP	25.44 (11.71, 39.18)	27.67 (16.51, 38.82)	18.41 (7.02, 29.80)	17.46 (8.71, 26.21)
Multiparity: ref=Nulliparity	10.13 (2.24, 18.02)	5.42 (–0.94, 11.77)	8.56 (2.20, 14.92)	6.04 (0.87, 11.21)
Gestational diabetes	7.34 (–4.88, 19.56)	–	6.37 (–3.51, 16.26)	3.99 (–3.07, 11.06)
Lactation duration (months)	0.16 (–1.06, 1.39)	1.31 (0.47, 2.16)	0.20 (–0.79, 1.19)	1.04 (0.35, 1.72)
Sedentary time (hours/day)	–0.92 (–2.99 ,1.16)	–1.39 (–2.84, 0.05)	–0.76 (–2.44, 0.92)	–
Poor sleep quality: ref=Good	0.40 (–8.60, 9.39)	–	1.58 (–5.70, 8.85)	3.97 (–1.24, 9.18)
Serum FBS	0 .25 (0.09, 0.41)	0.27 (0.14, 0.39)	0.20 (0.07, 0.33)	0.09 (–0.02, 0.21)
Serum LDL cholesterol	0.08 (–0.03, 0.20)	0.09 (0.01, 0.18)	0.08 (–0.01, 0.17)	0.07 (0.00, 0.14)
Log (UACR)	5.88 (2.40, 9.36)	–	5.27 (2.51, 8.03)	2.68 (0.34, 5.03)
Urine potassium/creatinine ratio	2.54 (0.69, 4.40)	1.83 (0.40, 3.26) Adjusted R^2=0.60	–1.03 (–2.35, 0.28)	–0.75 (–1.71, 0.21) Adjusted R^2=0.61

BMI=body mass index, FBS=fasting blood sugar, HDP=hypertensive disorder in pregnancy, LDL=low-density lipoprotein, UACR=urine microalbumin/creatinine ratio, Adj.=adjusted, coef.=coefficient, CI=confidence interval

Discussion

The study women with recent PE or GHT had higher blood pressure, higher hypertension rates, and higher serum hs-CRP, when compared to the normotensive women at the 6 weeks and 6-12 months postpartum study visits. For UACR, higher levels were found at 6-12 months postpartum in women in PE or CHT groups. We found no significant differences in behavioral measurements or other urinary biomarkers between the study groups. A history of PE and GHT was independently associated with increased systolic and diastolic blood pressures at both study visits in the final best-fitted model.

When compared to the normotensive women, women in the PE and GHT groups had elevated blood pressure at both the 6-week and 6-12-month postpartum visits. These findings are consistent with 6 weeks postpartum studies conducted in Nigeria and the United Kingdom[31,32], and with 1-year postpartum studies from Denmark, Norway, the United Kingdom, and the United States[8,17,21,33-35]. The majority of women in the PE group and all women in the GHT group who had hypertension at 6 weeks postpartum showed persistent hypertension at the 6-12 months postpartum visits in our study. This finding is in agreement with the physiology of pregnancy, that blood pressure generally returns to normal by 6 weeks postpartum[6,31]. Therefore, we suggest that women who have experienced HDP and who have retained or developed hypertension at 6 weeks postpartum should be advised about lifestyle interventions, regardless of their HDP subtype. According to hypertension practice guidelines, if a hypertensive blood pressure is still not well-controlled after 3-6 months of lifestyle intervention, antihypertensive treatment should be offered[36].

Our study found higher levels of serum hs-CRP in the PE and GHT groups at both postpartum study visits compared to the normotensive group, regardless of BMI. This finding is similar to the finding of a study in Norway in which HDP increased the odds of having postpartum hypertension and elevated hs-CRP in overweight and obese women[21]. However, this association was not found in other studies, although the average BMIs of the participating women were higher than in our study[33,34]. This discrepancy indicates a multifactorial mechanism of elevated hs-CRP after HDP pregnancies, not only related to BMI[37]. Increased UACR in women in the PE group at the 6-12 months postpartum study visit in our study is in agreement with a previous study of UACR one year after preeclampsia[33] and a systematic review including women in postpartum periods up to seven years[38]. The elevation of both serum hs-CRP and UACR in women following PE found in our study could be additionally used for monitoring cardiovascular risk in this group[35,39].

A history of PE or GHT in the index pregnancy was independently associated with elevated systolic and diastolic blood pressures at the 6 weeks and 6-12 months postpartum study visits, after adjusting for potential confounders. This finding is in agreement with a previous study conducted at three months and one year postpartum, to determine the association between HDP and postpartum BP using linear regression, but the coefficients were slightly different than ours, which may be due to variations in socioeconomic characteristics and other CVD risk factors[34]. The association between a history of PE and GHT and elevated blood pressure postpartum is clinically important, as shown by an earlier study identifying that each 20/10 mmHg difference in systolic/diastolic blood pressure was associated with a two-fold difference in cardiovascular morbidities and mortality[40].

The major strength of our study was that this was a longitudinal study measuring comprehensive biomarkers, physical and behavioral measurements, and standardized blood pressure measurements among women with previous HDP at two time-points postpartum, that are the time-points recommended in the ISSHP international guidelines for

CVD screening (6 weeks and 6–12 months after delivery)[20]. Also, this was, to our knowledge, the first study from Asia addressing postpartum CV risk following HDP. In addition, we used a standard definition of HDP with confirmation through medical records using prespecified criteria to avoid misclassification of the index pregnancy group.

There were some limitations in our study. Firstly, our data collection was carried out during the COVID-19 pandemic, which restricted postpartum visits and limited the rate of recruitment. Second, fear of travelling during the COVID-19 pandemic also led to a high rate of lost to follow-up at 6–12 months postpartum. Nevertheless, we found no significant differences in demographic and obstetrics information, physical and behavioral measurements, or biomarkers between the women lost to follow-up and those who participated at both postpartum time-points (Table 5). Thirdly, our study took place at two tertiary hospitals located in urban areas, introducing some degree of selection bias, as women from rural areas were under-sampled. However, this bias may be minimal due to the fact that pregnant women suspected of hypertensive disorders having antenatal care at other health facilities in rural areas were referred for ante- and intrapartum care at the study hospitals. Fourth, the number of participants with CHT was small compared to those in other HDP groups. Finally, the low number of participants with few postpartum hypertension cases limited further analyses of other factors associated with postpartum hypertension. Most behavioral measurements and biomarkers evaluated in our study were not consistently associated with blood pressure at both study visits, which may be due to the even smaller number of women at the second postpartum (6–12 months) study visit.

Table 5 Demographic and obstetrics information, physical and behavioral measures, and biomarkers at 6 weeks postpartum study visit by the completeness of follow-up

Variable	Completed follow-up (n=73)	Lost to follow-up (n=45)	Total (N=118)	p-value
Demographic and obstetrics information				
Index pregnancy group				0.31
Preeclampsia	23 (31.5)	17 (37.8)	40 (33.9)	
Gestational hypertension	14 (19.2)	13 (28.9)	27 (22.9)	
Chronic hypertension	8 (11.0)	2 (4.4)	10 (8.5)	
Normotensive	28 (38.4)	13 (28.9)	41 (34.7)	
Age (years), mean (S.D.)	33.3 (5.0)	31.8 (4.2)	32.8 (4.8)	0.099
Religion				0.813
Buddhism	37 (50.7)	25 (55.6)	62 (52.5)	
Islam	35 (47.9)	20 (44.4)	55 (46.6)	
Christian	1 (1.4)	0 (0.0)	1 (0.8)	
Education				0.419
Less than bachelor's degree	18 (24.7)	15 (33.3)	33 (28.0)	
Bachelor's degree or higher	55 (75.3)	30 (66.7)	85 (72.0)	
Underlying disease				
Chronic hypertension	10 (13.7)	6 (13.3)	16 (13.6)	1
Diabetes mellitus	2 (2.7)	0 (0.0)	2 (1.7)	0.524
Dyslipidemia	1 (1.4)	0 (0.0)	1 (0.8)	1
Family history				
Family history of hypertension	34 (46.6)	21 (46.7)	55 (46.6)	1
Family history of cardiovascular disease	12 (16.4)	3 (6.7)	15 (12.7)	0.206
Family history of HDP	8 (11.0)	4 (8.9)	12 (10.2)	1

Table 5 (continued)

Variable	Completed follow-up (n=73)	Lost to follow-up (n=45)	Total (N=118)	p-value
Pre-pregnancy BMI (kg/m^2), median (IQR)	24.1 (20.2, 28.6)	24.7 (21.4, 28.0)	24.3 (20.8, 28.4)	0.572
Characteristics of most recent pregnancy				
Nulliparity	36 (49.3)	23 (51.1)	59 (50.0)	1
Gestational diabetes	14 (19.2)	9 (20.0)	23 (19.5)	1
Preterm birth (<37 weeks of gestation)	13 (17.8)	9 (20.0)	22 (18.6)	0.957
Low birth weight infant (<2500 g)	13 (17.8)	8 (17.8)	21 (17.8)	1
SGA infant (<10th birth weight centile)	7 (9.6)	2 (4.4)	9 (7.6)	0.48
Physical and behavioral measures				
Postpartum duration (weeks), median (IQR)	6.9 (6.1, 7.4)	6.6 (6.1,8)	6.7 (6.1, 7.6)	0.584
Systolic blood pressure (mmHg), mean (S.D.)	122.0 (17.2)	120.0 (18.4)	121.2 (17.6)	0.548
Diastolic blood pressure (mmHg), mean (S.D.)	80.3 (13.2)	78.9 (15.1)	79.7 (13.9)	0.61
Current hypertension (≥140/90 mmHg, self-reported, treated)	21 (28.8)	11 (24.4)	32 (27.1)	0.764
Current prehypertension (120-139/80-89 mmHg)	30 (41.1)	15 (33.3)	45 (38.1)	0.517
Postpartum BMI (kg/m^2), mean (S.D.)	25.1 (22.5, 28.8)	25.2 (23.3, 28.6)	25.1 (22.7, 28.7)	0.492
Lactation duration (months), median (IQR)	1.6 (1.4,1.7)	1.5 (1.4, 1.8)	1.6 (1.4, 1.7)	0.75
Insufficient physical activity	63 (86.3)	38 (84.4)	101 (85.6)	0.993
Poor sleep quality (PSQI global score >5)	65 (89)	41 (91.1)	106 (89.8)	1
Biomarkers				
Serum FBS (mg/dL), median (IQR)	81.9 (78.3, 87)	82.0 (79.2, 89)	82.0 (78.5, 88.2)	0.528
Serum FBS categories (≥126 mg/dL)	2 (2.7)	2 (4.4)	4 (3.4)	0.635
Serum HbA1c (%), median (IQR)	5.2 (5.1, 5.6)	5.4 (5.2, 5.6)	5.3 (5.1, 5.6)	0.187
Serum HbA1c categories (≥6.5%)	1 (1.4)	3 (6.7)	4 (3.4)	0.154
Serum LDL cholesterol (mg/dL), median (IQR)	137.8 (111.0, 161.9)	144.8 (126.6, 167)	141.8 (119.2, 164.7)	
Serum LDL cholesterol categories (≥130 mg/dL)	43 (58.9)	31 (68.9)	74 (62.7)	0.372
Serum creatinine (mg/dL), median (IQR)	0.70 (0.63, 0.79)	0.67 (0.60, 0.74)	0.69 (0.62, 0.77)	0.193
Serum hs-CRP (mg/L), median (IQR)	2.4 (1.0, 4.2)	2.3 (1.2, 4.6)	2.4 (1.1, 4.3)	0.923
UACR (mg/g Cr), median (IQR)	8.4 (5.5, 25.2)	8.6 (4.7, 16.4)	8.5 (5.0, 24.3)	0.838
Urine sodium (mmol/L), mean (S.D.)	139.8 (53.0)	143.2 (56.4)	141.1 (54.1)	0.743
Urine sodium/creatinine ratio, median (IQR)	14.5 (8.8, 21.3)	14.7 (11.2, 19.9)	14.6 (9.4, 20.7)	0.595
Urine potassium (mmol/L), median (IQR)	45.0 (32.7, 54.4)	44.0 (30.0, 65.7)	44.9 (30.1, 55.9)	0.844
Urine potassium/creatinine ratio, median (IQR)	4.5 (2.6, 6.0)	4.8 (3.2, 6.4)	4.5 (2.7, 6.1)	0.227
Urine sodium/potassium ratio, median (IQR)	3.2 (1.9, 4.3)	3.1 (2.4, 3.8)	3.1 (2.3, 4.1)	0.951

Data are reported as n (%) unless stated otherwise
BMI=body mass index, Cr=creatinine, FBS=fasting blood sugar, HbA1c=glycated hemoglobin, HDP=hypertensive disorder in pregnancy, hs-CRP=high-sensitivity C-reactive protein, LDL=low-density lipoprotein, MET=metabolic equivalent of task, PSQI=Pittsburgh Sleep Quality Index, SGAL small for gestational age, UACR=urine microalbumin/creatinine ratio, S.D.=standard deviaion, IQR=interquartile range

Conclusion

In conclusion, women with a recent delivery complicated by PE or GHT experienced higher blood pressures and prevalences of hypertension, as well as higher levels of serum hs-CRP and UACR, at 6 weeks and 6-12 months postpartum. Hypertension diagnosed at 6 weeks postpartum mostly persisted at 6-12 months postpartum. Our findings emphasize the necessity of offering cardiovascular risk counselling and lifestyle interventions in women following PE and GHT, preferably as early as 6 weeks postpartum. The long-term effects of cardiovascular biomarkers on the future development of cardiovascular diseases should be further studied.

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Conflict of interest

The authors have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

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