Prevalence of Hypertensive Phenotypes After Preeclampsia
A Prospective Cohort Study

Agnès Ditisheim, Grégoire Wuerzner, Belen Ponte, Yvan Vial, Olivier Irion, Michel Burnier, Michel Boulvain, Antoinette Pechère-Bertschi

See Editorial Commentary, pp 59–60

Abstract—Preeclampsia is associated with increased cardiovascular and renal risk. The aim of this prospective cohort study was to characterize the early postpartum blood pressure (BP) profile after preeclampsia. We enrolled 115 women with preeclampsia and 41 women with a normal pregnancy in a prospective cohort study. At 6 to 12 week postpartum, we assessed the prevalence of different hypertensive phenotypes using 24-hour ambulatory BP monitoring (ABPM), as well as the risk of salt sensitivity and the variability of BP derived from ABPM parameters. Among patients with preeclampsia, 57.4% were still hypertensive at the office. Daytime ABP was significantly higher in the preeclampsia group (118.9±15.0/83.2±10.4 mm Hg) than in controls (104.8±7.9/71.6±5.3 mm Hg; $P<0.01$). Differences between groups were similar for nocturnal BP values. Fifty percent of preeclampsia women remained hypertensive on ABPM in the postpartum, of whom 24.3% were still under antihypertensive treatment; 17.9% displayed a white-coat hypertension and 11.6% had masked hypertension. In controls, 2.8% had white-coat hypertension; none had masked hypertension or needed hypertensive treatment. The prevalence of nondippers was similar 59.8% in the preeclampsia group versus 51.4% in controls. High-risk class of salt sensitivity of BP was increased in preeclampsia women (48.6%) compared with controls (17.1%); $P<0.01$. In conclusion, ABPM 6 to 12 weeks after delivery reveals a high rate of sustained ambulatory, nocturnal, and masked hypertension after preeclampsia. This finding may help identify women who should be included in a postpartum cardiovascular risk management program.

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Key Words: blood pressure ■ masked hypertension ■ postpartum period ■ preeclampsia ■ pregnancy

Preeclampsia is a hypertensive disorder specific to gestation that affects 5% to 8% of all pregnancies[1] and is associated with a greater lifetime risk for cardiovascular and renal complications.[2,3] Recently, different international guidelines have underlined that women who had a hypertensive disorder of the pregnancy should benefit from a postpartum screening and management for cardiovascular risk factors, but with no precise recommendations, especially about the timing of the first medical visit.[4–7] The existence and the prevalence of specific hypertensive phenotypes after preeclampsia is not known and the place of ambulatory blood pressure monitoring (ABPM) in the early follow-up of preeclampsia needs to be defined.

A blunted nocturnal dip of BP has been described in hypertensive disorders of pregnancy and seems to correlate with the severity of the disease.[8,9] Nocturnal hypertension in pregnancy has been associated with more maternal and fetal adverse outcomes, such as preeclampsia, renal insufficiency, severe hypertension, and low birth weight babies.[10] However, whether the nondipping pattern of BP persists during the postpartum period has never been investigated systematically.

In the present prospective study, we hypothesized that part of the elevated cardiovascular risk in women with a history of preeclampsia is partly related to the underdiagnosis of hypertension, in particular masked hypertension, and the persistence of abnormalities in the circadian profile of BP after pregnancy. To this purpose, we performed 24-hour ABPM in women with preeclampsia and in women with uncomplicated pregnancies (controls) to assess the different BP phenotypes 6 to 12 weeks after delivery. As abnormal circadian profile has been shown to be associated with increased salt sensitivity of BP,[11] we also estimated the risk of salt sensitivity (RSS) and the variability of the BP derived from ABPM parameters.

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From the Hypertension Centre (A.D., B.P., M. Boulvain, O.I., A.P.-B.), Service of Nephrology (B.P.), Department of Medical Specialties, and Service of Obstetrics (A.D., O.I., M. Boulvain), Department of Gynaecology and Obstetrics, University Hospitals of Geneva, Switzerland; and Service of Nephrology and Hypertension, Department of Medicine (G.W., M. Burnier) and Service of Obstetrics (Y.V.), Department of Gynaecology and Obstetrics, Lausanne University Hospital, Switzerland.

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Correspondence to Antoinette Pechère-Bertschi, Service of Endocrinology, Diabetology, Hypertension and Nutrition, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 4, Switzerland. E-mail antoinette.pechere@hcuge.ch

Methods

Study Type and Population

We performed a prospective cohort study in women with preeclampsia and a subgroup without preeclampsia. The main criteria for cases inclusion were preeclampsia during the index pregnancy, consent to participate and have a postpartum ABPM regardless of office BP values, drug treatment, and albuminuria. Main exclusion criteria were the use of anti-inflammatory drugs or any known cardiac, endocrine, or renal diseases. Inclusion criteria for the control group were healthy women who had an uncomplicated normotensive pregnancy, delivered spontaneously at term, consenting to participate and to have a postpartum ABPM.

The Ethics Committee of both institutions approved this study and written informed consent was obtained from each participant. Study was registered and performed according to the Helsinki declaration.

Study Procedure

All women were screened after delivery. If the study was accepted, they were evaluated at 6 to 12 week postpartum either at the Hypertension Unit of the University Hospital of Geneva or in the Service of Nephrology and Hypertension at Lausanne University Hospital, Switzerland. The timing of the visit was chosen to coincide with the gynecologic visit routinely performed after delivery. The participants came in the morning after a light snack. Height and weight were measured and body mass index calculated. Relevant maternal and infant medical histories and family factors were collected, and a complete physical examination was performed. Office BP and 24-hour ABPM were performed as described below. Plasma creatinine, spot urine albumin, and creatinine were measured, and kidney function was estimated using the CKD-EPI formula (Chronic Kidney Disease–Epidemiology Collaboration).[12]

Definitions

Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy statement of 2014, as new-onset hypertension after 20-week gestation associated with at least 1 end-organ damage.[13] Birth weight percentiles were determined according to the Swiss Society of Pediatrics standards, and small for gestational age infants were defined as a birth weight <10th percentile for gestational age at birth.

Hypertension phenotypes were defined as follows: masked hypertension was defined as normal office BP (<140/90 mm Hg) with high diurnal ABP (≥135/85 mm Hg) or nocturnal BP,[14] white-coat hypertension referred to high office BP (≥140/90 mm Hg) with normal awake ABP measurement (<135/85 mm Hg)[14]; sustained hypertension and true normotensive state described situations where both types of BP measurements were concordant. These definitions were used for both treated and untreated patients.

Normal dipping was defined as nocturnal drop of ≥10% to 20% of mean ABP. Nondippers were subjects with 0% to 9% nocturnal fall of mean ABP, extreme dippers with >20% nocturnal fall, and reverse dippers included patients with a nocturnal increase of mean ABP.[15]

Nocturnal hypertension was defined as night ABP ≥120/70 mm Hg.

BP Measurement Methods

Office BP was measured according to European Society of Hypertension guidelines.[14] After 5 minutes of rest, 2 BP measurements were taken at 1 to 2 minute intervals, on the same arm, with a proper cuff size adjusted to the arm diameter and a validated automated device (Omron HEM-907-E; British Hypertension Society Grade A/A). Arithmetic mean of the 2 BP values was used for the present analysis.

A 24-hour ABPM was performed with a validated device (Diasys Integra, Physicor, Switzerland) and programmed to measure BP every 20 minutes from 07:00 to 22:59 and every 30 minutes from 23:00 to 06:59. Calibration of the device was made by 2 simultaneous auscultatory BP measurements, using a calibrated mercury sphygmomanometer connected to the ambulatory device by a Y tube. A difference of >5 mm Hg was considered acceptable.

Subjects were instructed not to smoke or drink alcohol or any caffeine-containing beverage, to record their time of sleep and awakening, as well as their activities in a diary. According to the European Society of Hypertension recommendations, ABPM was considered valid and was included in the analysis when at least 20 BP measurements during the day and 7 readings during the night were recorded.

Assessment of Salt Sensitivity Risk Using ABPM Data

We also estimated the RSS of BP with the formula of Castiglioni et al[16] that we validated previously in women with a history of severe preeclampsia.[17] Briefly, 3 classes of RSS graded as low, intermediate, and high, were defined based on the dipping status as described above and on the mean heart rate (HR) over 24 hours.

They were then classified as high HR and low HR when the 24-hour mean HR was respectively over or under 70 bpm. Low RSS included subjects classified as dippers and low 24-hour mean HR. Patients identified as nondippers with a high 24-hour mean HR were considered as high RSS class, and the intermediate RSS included all other subjects not otherwise classified.

Statistical Analysis

We compared women with and without preeclampsia. A secondary analysis restricted to white women, nonsmoker, with a body mass index <25 kg/m^2, and without past history of chronic hypertension was performed. Results are reported as a mean (SD) for continuous variables and in % (absolute number) for the categorical variables. Normality of the distribution was tested by drawing a histogram and Q-Q plot. Continuous variables were analyzed using a Student *t* test or Kruskal–Wallis and proportions using either the χ^2 or the Fisher test. A 2-sided *P* value of ≤0.05 was considered as statistically significant. All data analyses were performed with Stata software, version 12.1.

Results

Between July 2010 and December 2013, we screened 250 preeclampsia women at time of delivery, of which 115 gave their consent and had an ABPM done at 6 to 12 weeks postpartum. We also included 41 nonpreeclamptic healthy control women (Figure 1). Eight women were excluded for invalid recording (3 in the preeclampsia group and 5 in the controls). Among preeclampsia women, 57.4% (66/115) were still hypertensive at the office and 41.7% were albuminuric. At time of evaluation, 28 women (24.3%) were still under antihypertensive therapy (labetalol or nifedipine). The baseline characteristics of the groups at the postpartum visit are shown in Table 1. There were no significant differences between women with preeclampsia and controls for age, primiparity, prevalence of pregestational diabetes mellitus, and twin pregnancies. Several characteristics were significantly more prevalent or increased in the group of preeclamptic women: Afro-Caribbean origin (*P*<0.01), high body mass index (*P*<0.01), chronic hypertension before the index pregnancy (*P*=0.01), and smokers (*P*<0.01). All women were breastfeeding.

Preterm delivery was more frequent among women with preeclampsia compared with normal pregnancy (mean gestational age

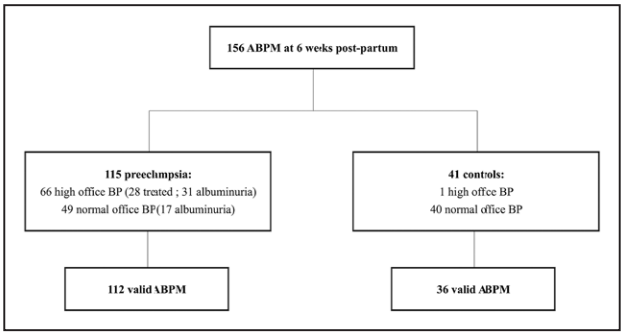

Figure 1. Flow chart. ABPM indicates ambulatory blood pressure monitoring; and BP, blood pressure.

Table 1. Baseline Characteristics of Patients

Characteristics	Preeclampsia (n=115)	Controls (n=41)	*P* Value
Age, y	33.7±5.7	33.2±6.7	0.6
Ethnic group			<0.01
White	58.3 (67)	97.6 (40)	
Afro-Caribbean	27.0 (31)	0.0 (0)	
Hispanic	9.6 (11)	0.0 (0)	
Asian	5.2 (6)	2.4 (1)	
Pregestational BMI, kg/m^2	25.4±5.2	22.3±3.3	<0.01
Smokers	16.5 (19)	0.0 (0)	<0.01
Chronic hypertension	13.9 (16)	0.0 (0)	0.01
Pregestational diabetes mellitus	4.34 (5)	0.0 (0)	0.14
Primiparity	60.0 (69)	53.7 (22)	0.5
Twin pregnancy	7.0 (8)	0.0 (0)	0.2
Caesarean section	49.6 (57)	0.0 (0)	<0.01
Birth gestational age, wk	36.0±3.9	39.4±1.6	<0.01
Birth weight, g (n=125)	2525.6±898.1	3230±449.9	<0.01
Urine albuminuria, mg/L	96.2±453.4	18.6±35.7	<0.01
ACR, mg/mmol	11.3±64.8	<detection limit	<0.01

Data are expressed in mean±SD or % (absolute) and analyzed using Student *t* test, Kruskal–Wallis test, Fisher test or the χ^2 test as appropriate. ACR indicates urinary albumin on creatinine ratio; and BMI, body mass index.

Table 2. Office and 24-Hour Ambulatory Blood Pressures

Parameters	Preeclampsia (n=115)*	Controls (n=41)*	*P* Value
Office measurements			
Office BP systolic	130.4±14.1	107.7±10.3	<0.01
Office BP diastolic	89.7±11.5	69.2±9.0	<0.01
Heart rate, bpm	77.8±9.9	74.4±8.8	0.1
Diurnal ABP			
ABP, systolic	118.9±15.0	104.8±7.9	<0.01
ABP, diastolic	83.2±10.4	71.6±5.3	<0.01
Pulse pressure	36.5±9.6	33.1±4.8	0.1
Heart rate, bpm	83.6±9.2	79.4±7.2	0.01
SD, systolic	13.8±4.7	10.8±4.5	<0.01
SD, diastolic	11.4±6.1	8.7±2.4	0.01
Nocturnal ABP			
ABP, systolic	111.2±17.6	94.3±7.6	<0.01
ABP, diastolic	74.8±11.0	61.7±4.6	<0.01
Pulse pressure	36.6±11.1	32.5±6.0	0.03
Heart rate, bpm	72.0±10.6	60.0±6.7	<0.01
SD, systolic	11.0±4.5	9.1±2.1	0.01
SD, diastolic	9.8±3.3	8.0±2.0	<0.01

Data are expressed in mean±SD or % (absolute) and analyzed using the Student *t* test or Kruskal–Wallis as appropriate. Values are in mm Hg unless specified otherwise. ABP indicates ambulatory blood pressure; and BP, blood pressure.

*Three (preeclampsia group), respectively 5 (controls) recordings were considered invalid.

at birth, 36.0±3.9 versus 39.4±1.6 weeks; *P*<0.01). Accordingly, birth weight of the newborns in the preeclampsia group was significantly lower (2525.6±898.1 versus 3230.0±449.9 g; *P*<0.01). However, there was no significant difference between groups in terms of small for gestational age infants (birth weight <10th percentile for gestational age). Of note, 7 neonatal deaths (6.1%) occurred in the group with preeclampsia.

Office BP and 24-hour ambulatory BP values are shown in Table 2. Office BP was significantly higher among women who had preeclampsia than in controls. Daytime systolic and diastolic ABP were significantly higher in the preeclampsia group (118.9±15.0/83.2±10.4 mm Hg) than in the control group (104.8±7.9/71.6±5.3 mm Hg; *P*<0.01). Nighttime ABP was also significantly higher in the preeclampsia group (111.2±17.6/74.8±11.0 mm Hg) compared with the control group (94.3±7.6/61.7±4.6 mm Hg). The SD of the systolic and diastolic daytime ABP, a proxy of the variability of the BP,[18] was significantly higher in the preeclampsia group (13.8±4.7/11.4±6.1 mm Hg) than in controls (10.8±4.5/8.7±2.4 mm Hg; *P*=0.01), so were the nighttime values (11.0±4.5/9.8±3.3 mm Hg in preeclampsia, and 9.1±2.1/8.0±2.0 mm Hg in controls; *P*<0.01). Table 3 presents the different BP phenotypes. Among preeclampsia women without treatment, 23.8% (20/84) of them had a confirmed diurnal high ABP (≥135/85 mm Hg) at 6 to 12 week postpartum compared with 0.0% in the controls, *P*<0.01. Prevalence of white-coat hypertension was also significantly increased (17.9%) compared with controls (2.8%; *P*<0.01). Masked hypertension was more frequent in preeclampsia group (11.6%) than in the controls (0.0%; *P*<0.01). Nocturnal hypertension (nighttime ABP ≥120/70 mm Hg) in patient with normal office BP was more frequent in preeclampsia women (33.6% [36/107] versus 2.9% [1/35] in controls; *P*<0.01). Furthermore, among the 28 patients still requiring antihypertensive treatment 6 to 12 week after preeclampsia, 17.9% had white-coat hypertension and 17.9% masked hypertension. Systolic and diastolic BP patterns are illustrated in Figures 2 and 3.

In preeclampsia women, normal nocturnal dipping was lost in 59.8% of patients, of whom 45.8% were nondippers, 10.3% were reversed dippers, and 3.7% were extreme dippers. In the control group, 51.4% were nondippers but still in the normal range of ABP values, and 11.4% were extreme dippers. We also calculated the salt sensitivity risk index.[17] Indeed, 48.6% of preeclampsia women were categorized as high risk for salt sensitivity compared with only 17.1% of the control group (*P*<0.01).

We performed a secondary analysis restricted to white, non smoker, with a body mass index <25 kg/m^2, and no past history of chronic hypertension and found similar results (Tables S1 and S2 in the online-only Data Supplement).

Discussion

The main finding of this study is that women who had preeclampsia have a high prevalence of persistent diurnal and nocturnal ambulatory hypertension 6 to 12 weeks after delivery. In addition, preeclampsia is associated with an increased prevalence

Table 3. Patterns of High Blood Pressure and Salt Sensitivity Risk

Patterns of BP	Preeclampsia (n=115)*	Controls (n=41)*	*P* Value
Ambulatory BP without treatment (n=87)*			<0.01
Normal ABP % (absolute)	48.8 (41/84)	97.2 (35/36)	
HTN (ABP ≥135/85 mm Hg)	23.8 (20/84)	0.0 (0/36)	
White-coat HTN	17.9 (15/84)	2.8 (1/36)	
Masked HTN	9.5 (8/84)	0.0 (0/36)	
Ambulatory BP with treatment (n=28)			
Controlled HTN	14.3 (4/28)	N/A	N/A
Uncontrolled HTN	50 (14/28)		
White-coat HTN	17.9 (5/28)		
Masked HTN	17.9 (5/28)		
Categories of hypertension on 24-h ABP			<0.01
Systolic	2.7 (3/112)	0	
Diastolic	28.6 (32/112)	2.8 (1/36)	
Systolo-diastolic	15.2 (17/112)	0	
Nocturnal HTN†	64.5 (69/107)	2.9 (1/35)	
Mean circadian rhythm (n=107)†			0.07
Dippers, %	40.2 (43/107)	48.6 (16/35)	
Nondippers, %	45.8 (49/107)	40.0 (14/35)	
Extreme dippers, %	3.7 (4/107)	11.4 (4/35)	
Reverse dippers, %	10.3 (11/107)	0.0 (0/35)	
Salt sensitivity risk (n=107)†			<0.01
Low risk, %	3.7 (4/107)	14.3 (5/35)	
High risk, %	48.6 (52/107)	17.1 (6/35)	
Intermediate risk, %	47.6 (51/107)	68.6 (24/35)	

Data are expressed in % (absolute) and analyzed using the χ^2 test. ABP indicates ambulatory blood pressure; and HTN, hypertension.

*Three (preeclampsia group), respectively 5 (controls) recordings were considered invalid.

†Five (preeclampsia group), respectively 1 (controls) nocturnal recordings were considered insufficient for analysis.

of postpartum white-coat and masked hypertension. The index of salt sensitivity risk and the variability of ambulatory BP as reflected by the SDs, a proxy of variability, were significantly increased in preeclampsia women compared to controls.

Preeclampsia is associated with an increased long-term risk of hypertension, cardiovascular and renal diseases, and diabetes mellitus.[19] Recently, guidelines of the American Heart Association and of the European Societies of Hypertension and Cardiology emphasized the need for an appropriate postpartum screening and control of the cardiovascular risk factors for women with a history of hypertensive disorder of pregnancy.[14,20] However, specific data on the management of the early follow-up after preeclampsia are lacking and ABPM in the postpartum period has never, to our knowledge, been evaluated. In clinical practice, ABPM has been shown to be a useful and cost effective tool for establishing true diagnosis of hypertension, as well as detecting masked and white-coat hypertension.[14,21]

Our study shows that ABPM detects a large diversity of BP phenotypes in the postpartum of preeclampsia women. Among women who had preeclampsia, 50% of them have a persistent ambulatory true hypertension when measured 6 to 12 weeks postpartum outside the office. Among the 28 patients under treatment, ABPM revealed that 14 (50%) of them were not controlled and allowed the interruption of 5 (17.9%) treatments.

Studies on hypertensive disorders of pregnancy have focused on antepartum period and unfortunately only few studies addressed the issue of hypertension in the postpartum.[22] It is usually believed that many of the postpartum abnormalities of preeclampsia women progressively disappear.

In our study, 17.9% of women with preeclampsia presented with a white-coat hypertension. In some studies, white-coat hypertension was associated with a modest increased risk of stroke and target organ damage in the general population.[23–25] In the particular condition of pregnancy, white-coat hypertension identified early during pregnancy has been associated with a slightly increased risk incidence of preeclampsia but with a better pregnancy outcome than pregnancy complicated by chronic hypertension.[26,27] If the optimal management of white-coat hypertension is uncertain, especially in the postpartum period, its identification may prevent unnecessary use of antihypertensive medication.

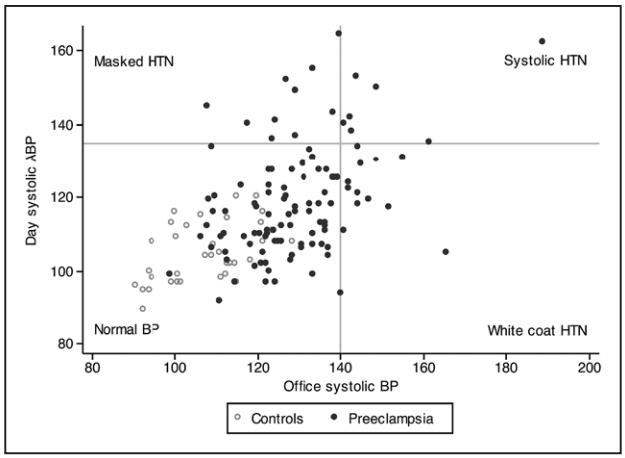

Figure 2. Hypertension patterns among groups: daytime systolic blood pressure (BP). ABP indicates ambulatory blood pressure; and HTN, hypertension.

We also found that 11.6% (13/112) of women who had preeclampsia with a normal office BP, had masked hypertension in the postpartum. Masked hypertension has been associated with a higher long-term cardiovascular risk and an increased rate of target organ damage similar to sustained hypertension.[23,28–30] Albuminuria is an important cardiovascular risk factor and has been shown to be increased in subjects with masked hypertension.[31–33] In our study, ABPM revealed a masked hypertension in 13.0% of patients with albuminuria and in 10.6% nonalbuminuric women (P=0.6). To the best of our knowledge, masked hypertension has never been described after preeclampsia, in particular, in the event of persisting albuminuria. This could represent another link between cardiovascular disease and preeclampsia.[23,28,34] Considering the potential long-term consequences for the mother, masked hypertension in the postpartum needs closer attention.

Nondipping profile is also associated with an increased cardiovascular risk and target organ damage. Early studies on circadian variations of BP during preeclampsia showed the loss of the normal nocturnal fall and this was correlated to the severity of the disease.[9] In a previous article, we observed the persistence of the nondipper status up to 10 years after

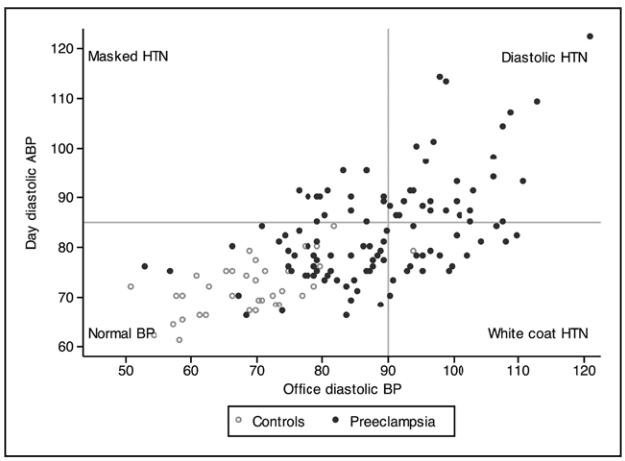

Figure 3. Hypertension patterns among groups: daytime diastolic blood pressure (BP). ABP indicates ambulatory blood pressure; and HTN, hypertension.

preeclampsia.[17] In the present study, we found that early after preeclampsia, 59.8% of women had an abnormal nocturnal dipping, and among them, 10.3% had a reversed circadian rhythm. The control group also displayed a nondipper pattern, however absolute nocturnal BP values were low (94.3±7.6/61.7±4.6 mm Hg in the control group versus 111.2±17.6/74.8±11.0 mm Hg in the preeclampsia group). Sleep disruption of the breastfeeding mother may explain the absence of nocturnal BP drop in both groups.

Salt sensitivity of BP is defined as an increase of 5% to 10% of office BP or of ≥4 mm Hg of the mean ambulatory BP after a high salt intake.[35] Salt sensitive profile is a known cardiovascular and renal risk factor independent of hypertension and is associated with lack of nocturnal BP fall.[36,37] We previously showed that women with a history of severe preeclampsia had an increased salt sensitivity of the ABP and a lack of nocturnal dipping compared with uncomplicated pregnancies, 10 years after the event.[17] We also validated the formula derived from ABPM parameters to estimate the RSS of Castiglioni et al,[16] in a group of preeclamptic women by assessing the salt sensitivity with a gold standard protocol. In the present study, 48.6% of women who had preeclampsia were classified as having a high RSS in the postpartum period versus 17.1% in the control group. Elevated nocturnal BP may result from a defect in diurnal salt excretory capacity of the kidneys, with a shift of the pressure natriuresis curve to the right at night.[38] The kidney is an organ primarily damaged in preeclampsia, and consequently, the ability to maintain sodium balance may be altered in the postpartum period and later in life.[17] This suggests that, in addition to lifestyle modifications, a low salt strategy may be beneficial to women who remain hypertensive after preeclampsia.

The increased short-term BP variability on 24-hour ABPM is known to be an independent risk factor for cardiovascular events and has been associated with arterial stiffness, stroke, and heart damage and salt sensitivity of the BP.[39] Preeclamptic women in our work displayed a significantly higher SD of the ambulatory daytime and nighttime systolic and diastolic BP suggesting a higher BP variability after preeclampsia when compared with normal pregnancies.

Together, the high ambulatory BP, the lack of nocturnal dipping, and the increased salt sensitivity index, may contribute to the higher morbidity of preeclamptic women observed later in life. Although difficult to evaluate with certainty, a proportion of women with persisting postpartum hypertension might have had unrecognized preexisting hypertension superimposed by preeclampsia. Women who had preeclampsia also seem to share mechanisms usually evoked for BP variability and salt sensitivity with people with increased cardiovascular risk.

We have to acknowledge several limitations in our study. First is the lack of homogeneity in the ethnic origin of patients between groups, as well as for the body mass index, tobacco use, and past history of hypertension. These characteristics are known risk factors for preeclampsia,[40,41] except for smoking, and are therefore more represented in the preeclampsia group. However, the secondary analysis excluding women with these potential confounders showed similar results (Tables S1 and S2). Second, the small size of our control group can be explained by a low rate of participation by women who had

an uncomplicated pregnancy. As the follow-up was demanding (ABPM, urine and blood tests, medical visits), it was more difficult to motivate them to come back to the hospital for study purposes. However, even in the preeclampsia group, the rate of refusal was important (>50%). Therefore, we cannot exclude a selection bias affecting both groups, but as we showed a large and statistically significant difference, we think it is not necessary to increase the number of unaffected women. Another limitation may be the fact that parameters were measured only at 6 to 12 weeks and not later in the follow-up of preeclampsia women. Indeed, there is still a possibility that some of the BP phenotypes improve up to 6 months after pregnancy.

We present, to the best of our knowledge, the first study on the use of 24-hour ABPM in the early follow-up after preeclampsia. We demonstrate that 24-hour ABPM in the postpartum is useful to discriminate between fixed ambulatory hypertension, requiring close follow-up and possible treatment, from the white-coat hypertension. Moreover, it allows detection of masked hypertension, particularly in patients with persistent albuminuria and offers analysis of nondipper status after preeclampsia, pointing on possible salt sensitivity and renal damage.

The timing of assessment at 6 to 12 weeks postpartum is one of the strengths of our study. Indeed, even though hypertension may resolve during the first year following delivery, there is no reason for letting hypertensive women without care for >1 year. In our opinion, it is not justified to wait for complications or organ damages to happen before initiating effective preventive measures. International expert societies recommend careful follow-up of women with preeclampsia but clear guidelines on the modalities of this follow-up are still lacking.[4,6,42] Recently, published works encourage identification of high-risk women early after preeclampsia.[43,44] The group of Visser et al[44] showed that among 187 women who had a hypertensive disorder of pregnancy, 40% had hypertension at 6 weeks postpartum. Of interest, of these women, 61% still had hypertension 2.5 years postpartum.

In conclusion, we show that 24-hour ABPM is a valuable tool in the follow-up of preeclampsia. It enables to discriminate women with fixed ambulatory hypertension from those with white-coat hypertension and to identify masked hypertension and nondipper status.

As these hypertensive phenotypes are associated with a higher risk for cardiovascular disease later in life, performing a 24-hour ABPM after preeclampsia may be useful to identify women in whom one should implement early lifestyle modifications to prevent the development of hypertension and its complications. The impact of these on future cardiovascular events remains of course to be determined in prospective trials.

Perspectives

In this study, we show that 24-hour ABPM is a valuable tool in the follow-up of preeclampsia. It discriminates between fixed ambulatory hypertension and white-coat hypertension and identifies masked hypertension and nondipper status. The use of 24-hour ABPM helps to identify patients at risk for cardiovascular disease later in life and allows early implementation of lifestyle modifications. Further studies are required to guide clinical management of cardiovascular prevention in this population.

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Disclosures

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References

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170:1–7. doi: 10.1016/j.ejogrb.2013.05.005.
2. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008;156:918–930. doi: 10.1016/j.ahj.2008.06.042.
3. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2:e323–e333. doi: 10.1016/S2214-109X(14)70227-X.
4. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. 2013;122:1122–1131. doi: 10.1097/01.AOG.0000437382.03963.88.
5. National Institute for Health and Clinical Excellence: Guidance. *Hypertension in pregnancy: the management of hypertensive disorders during pregnancy*. London: RCOG Press; 2010.
6. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, Paech M, Said JM. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol*. 2015;55:e1–e29.
7. Mounier-Vehier C, Amar J, Boivin JM, Denolle T, Fauvel JP, Plu-Bureau G, Tsatsaris V, Blacher J. Hypertension artérielle et grossesse. Consensus d'experts de la Société française d'hypertension artérielle, filiale de la Société française de cardiologie. *Presse Med*. 2016;45:682–699. doi: 10.1016/j.lpm.2016.05.012.
8. Halligan A, Shennan A, Lambert PC, de Swiet M, Taylor DJ. Diurnal blood pressure difference in the assessment of preeclampsia. *Obstet Gynecol*. 1996;87:205–208. doi: 10.1016/0029-7844(95)00379-7.
9. Benedetto C, Zonca M, Marozio L, Dolci C, Carandente F, Massobrio M. Blood pressure patterns in normal pregnancy and in pregnancy-induced hypertension, preeclampsia, and chronic hypertension. *Obstet Gynecol*. 1996;88(4 pt 1):503–510.
10. Brown MA, Davis GK, McHugh L. The prevalence and clinical significance of nocturnal hypertension in pregnancy. *J Hypertens*. 2001;19:1437–1444.
11. Higashi Y, Oshima T, Ozono R, Nakano Y, Matsuura H, Kambe M, Kajiyama G. Nocturnal decline in blood pressure is attenuated by NaCl loading in salt-sensitive patients with essential hypertension: noninvasive 24-hour ambulatory blood pressure monitoring. *Hypertension*. 1997;30(2 pt 1):163–167.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
13. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens*. 2014;2:97–104. doi: 10.1016/j.preghy.2014.02.001.
14. Mancia G, Fagard R, Narkiewicz K, et al. Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eht151.
15. O'Brien E, Parati G, Stergiou G, et al; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31:1731–1768. doi: 10.1097/HJH.0b013e328363e964.

16. Castiglioni P, Parati G, Brambilla L, Brambilla V, Gualerzi M, Di Rienzo M, Coruzzi P. Detecting sodium-sensitivity in hypertensive patients: information from 24-hour ambulatory blood pressure monitoring. *Hypertension*. 2011;57:180–185. doi: 10.1161/HYPERTENSIONAHA.110.158972.
17. Martillotti G, Ditisheim A, Burnier M, Wagner G, Boulvain M, Irion O, Pechère-Bertschi A. Increased salt sensitivity of ambulatory blood pressure in women with a history of severe preeclampsia. *Hypertension*. 2013;62:802–808. doi: 10.1161/HYPERTENSIONAHA.113.01916.
18. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948. doi: 10.1016/S0140-6736(10)60309-1.
19. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974. doi: 10.1136/bmj.39335.385301.BE.
20. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262. doi: 10.1161/CIR.0b013e31820faaf8.
21. National Clinical Guideline Centre (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34 [Internet]. London: Royal College of Physicians (UK); 2011 Aug. https://www.ncbi.nlm.nih.gov/books/NBK83274/.
22. Magee L, von Dadelszen P. Prevention and treatment of postpartum hypertension. *Datab Syst Rev*. 2013:4:CD004351.
23. Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. *Am J Hypertens*. 2011;24:52–58. doi: 10.1038/ajh.2010.203.
24. Mancia G, Bombelli M, Brambilla G, Facchetti R, Sega R, Toso E, Grassi G. Long-term prognostic value of white coat hypertension: an insight from diagnostic use of both ambulatory and home blood pressure measurements. *Hypertension*. 2013;62:168–174. doi: 10.1161/HYPERTENSIONAHA.111.00690.
25. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. *J Hypertens*. 2016;34:593–599. doi: 10.1097/HJH.0000000000000832.
26. Bar J, Maymon R, Padoa A, Wittenberg C, Boner G, Ben-Rafael Z, Hod M. White coat hypertension and pregnancy outcome. *J Hum Hypertens*. 1999;13:541–545.
27. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. *BJOG*. 2005;112:601–606. doi: 10.1111/j.1471-0528.2004.00516.x.
28. Angeli F, Reboldi G, Verdecchia P. Masked hypertension: evaluation, prognosis, and treatment. *Am J Hypertens*. 2010;23:941–948. doi: 10.1038/ajh.2010.112.
29. Kotsis V, Stabouli S, Toumanidis S, Papamichael C, Lekakis J, Germanidis G, Hatzitolios A, Rizos Z, Sion M, Zakopoulos N. Target organ damage in "white coat hypertension" and "masked hypertension". *Am J Hypertens*. 2008;21:393–399. doi: 10.1038/ajh.2008.15.
30. Bobrie G, Clerson P, Ménard J, Postel-Vinay N, Chatellier G, Plouin PF. Masked hypertension: a systematic review. *J Hypertens*. 2008;26:1715–1725. doi: 10.1097/HJH.0b013e3282fbcedf.
31. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001;286:421–426.
32. Ishikawa J, Hoshide S, Eguchi K, Schwartz JE, Pickering TG, Shimada K, Kario K. Masked hypertension defined by ambulatory blood pressure monitoring is associated with an increased serum glucose level and urinary albumin-creatinine ratio. *J Clin Hypertens (Greenwich)*. 2010;12:578–587. doi: 10.1111/j.1751-7176.2010.00286.x.
33. Tomiyama M, Horio T, Yoshii M, Takiuchi S, Kamide K, Nakamura S, Yoshihara F, Nakahama H, Inenaga T, Kawano Y. Masked hypertension and target organ damage in treated hypertensive patients. *Am J Hypertens*. 2006;19:880–886. doi: 10.1016/j.amjhyper.2006.03.006.
34. Mallion JM, Clerson P, Bobrie G, Genes N, Vaisse B, Chatellier G. Predictive factors for masked hypertension within a population of controlled hypertensives. *J Hypertens*. 2006;24:2365–2370. doi: 10.1097/01.hjh.0000251895.55249.82.
35. Felder RA, White MJ, Williams SM, Jose PA. Diagnostic tools for hypertension and salt sensitivity testing. *Curr Opin Nephrol Hypertens*. 2013;22:65–76. doi: 10.1097/MNH.0b013e32835b3693.
36. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension*. 2001;37(2 pt 2):429–432.
37. Morimoto A, Uzu T, Fujii T, Nishimura M, Kuroda S, Nakamura S, Inenaga T, Kimura G. Sodium sensitivity and cardiovascular events in patients with essential hypertension. *Lancet*. 1997;350:1734–1737. doi: 10.1016/S0140-6736(97)05189-1.
38. Fujii T, Uzu T, Nishimura M, Takeji M, Kuroda S, Nakamura S, Inenaga T, Kimura G. Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. *Am J Kidney Dis*. 1999;33:29–35.
39. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol*. 2013;10:143–155. doi: 10.1038/nrcardio.2013.1.
40. Bryant AS, Seely EW, Cohen A, Lieberman E. Patterns of pregnancy-related hypertension in black and white women. *Hypertens Pregnancy*. 2005;24:281–290. doi: 10.1080/10641950500281134.
41. Wolf M, Shah A, Jimenez-Kimble R, Sauk J, Ecker JL, Thadhani R. Differential risk of hypertensive disorders of pregnancy among Hispanic women. *J Am Soc Nephrol*. 2004;15:1330–1338.
42. Redman CW. Hypertension in pregnancy: the NICE guidelines. *Heart*. 2011;97:1967–1969. doi: 10.1136/heartjnl-2011-300949.
43. Levine LD, Nkonde-Price C, Limaye M, Srinivas SK. Factors associated with postpartum follow-up and persistent hypertension among women with severe preeclampsia. *J Perinatol*. 2016;36:1079–1082. doi: 10.1038/jp.2016.137.
44. Visser VS, Hermes W, Franx A, Koopmans CM, van Pampus MG, Mol BW, de Groot CJ. High blood pressure six weeks postpartum after hypertensive pregnancy disorders at term is associated with chronic hypertension. *Pregnancy Hypertens*. 2013;3:242–247. doi: 10.1016/j.preghy.2013.07.002.

Novelty and Significance

What Is New?

- The use of 24-hour ambulatory blood pressure (BP) monitoring compared with office BP after preeclampsia has never been studied.

What Is Relevant?

- Masked hypertension is more frequent in women with a recent history of preeclampsia.
- Twenty-four–hour ambulatory BP monitoring is a valuable follow-up tool for pregnancy related hypertensive disorders. It enables detection of women at high risk for cardiovascular disease later in life and to target subgroups of women for whom prevention has to be intensively implemented.

Summary

Hypertensive phenotypes have a high prevalence in the early postpartum period after preeclampsia. Postpartum 24-hour ambulatory BP monitoring helps to discriminate between fixed and white-coat hypertension, detects masked hypertension, and identifies nondipper status pointing on possible salt sensitivity pattern. The use of 24-hour ambulatory BP monitoring in the postpartum is a valuable follow-up tool for pregnancy related hypertensive disorders. It allows early identification of phenotypes of BP at risk and helps the management of high-risk women.

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PREVALENCE OF HYPERTENSIVE PHENOTYPES AFTER PREECLAMPSIA: A PROSPECTIVE COHORT STUDY

Agnès Ditisheim[1,5], Grégoire Wuerzner[2], Belen Ponte[3,1], Yvan Vial[4], Olivier Irion[5,1], Michel Burnier[2], Michel Boulvain[5,1], Antoinette Pechère-Bertschi[1]

[1]Hypertension Centre, University Hospitals of Geneva, [2]Service of Nephrology and Hypertension, Lausanne University Hospital, [3]Service of Nephrology, University Hospitals of Geneva, [4]Service of Obstetrics, Lausanne University Hospital, [5]Service of Obstetrics, University Hospitals of Geneva, Switzerland

Short title: Hypertensive phenotypes after preeclampsia

Correspondence to:
Pechère-Bertschi Antoinette
Service of Endocrinology, Diabetology, Hypertension and Nutrition
University Hospitals of Geneva
Rue Gabrielle-Perret-Gentil 4
1211 Geneva 4 – Switzerland
Telephone / fax: + 41 22 372.93.02 / + 41 22 372.93.26
e-mail: antoinette.pechere@hcuge.ch

Table S1. Baseline characteristics of patients*

Characteristics	Preeclampsia (n=23)	Controls (n=33)	*p*
Age, y	34.9 ± 6.4	33.1 ± 7.1	0.3
Pregestational BMI, kg/m^2	22.1 ± 2.1	21.3 ± 2.2	0.2
Pregestational diabetes	4.35 (1)	0.0 (0)	0.2
Primiparity	82.6 (19)	57.6 (19)	0.05
Twin pregnancy	8.7 (2)	0.0 (0)	0.2
Cesarean	45.5 (10)	0.0 (0)	< 0.01
Birth gestational age, wk	35.6 ± 4.5	39.7 ± 1.4	< 0.01
Birth weight, grams (n=125)	2259.8 ± 964.5	3243.5 ± 450.3	< 0.01
Neonatal death	4.4 (1)	0.0 (0)	0.2
Urine Albuminuria, mg/L	20.1 ± 17.0	19.9 ± 37.6	0.2
ACR, mg/mmol	2.7 ± 2.4	1.5 ± 1.4	0.04

* Restricted for the ethnic group (Caucasian), BMI < 25kg/m^2, non-smokers, lack of personal history of chronic hypertension.

Abbreviations are: BMI, body mass index, ACR, urinary albumin on creatinine ratio.

Data are expressed in mean ± standard deviation or percentage (absolute) and analyzed using the Kruskal Wallis test, Fisher test or the Chi^2 test as appropriate.

Table S2. Office and 24h ambulatory blood pressures[*]

Parameters	Preeclampsia (n=23[†])	Controls (n=33[†])	*p*
Office measurements			
Office BP systolic	129.3 ± 11.4	107.9 ± 10.3	< 0.01
Office BP diastolic	89.4 ± 9.2	70.0 ± 8.7	< 0.01
Heart rate, bpm	74.7 ± 6.5	73.5 ± 9.2	0.6
Ambulatory BP			< 0.01
Normal ABP % (absolute)	36.4 (8/22)	96.7 (29/30)	
HTN (ABP ≥135/85 mmHg)	31.8 (7/22)	0.0 (0/30)	
White coat HTN	27.3 (6/22)	3.3 (1/30)	
Masked HTN	4.6 (1/22)	0.0 (0/30)	
Mean circadian rhythm[‡]			0.06
Dippers, %	36.4 (8/22)	51.7 (15/29)	
Non dippers, %	54.6 (12/22)	34.5 (10/29)	
Extreme dippers, %	0.0 (0/22)	13.8 (4/29)	
Reverse dippers, %	9.1 (2/22)	0.0 (0/29)	
Salt-Sensitivity Risk[‡]			0.02
Low-risk, %	0.0 (0/22)	17.2 (5/29)	
High-risk, %	45.5 (10/22)	17.2 (5/29)	
Intermediate risk, %	54.6 (12/22)	65.5 (19/29)	

[*] Restricted for the ethnic group (Caucasian), BMI < 25kg/m^2, non-smokers, lack of personal history of chronic hypertension.

[†] 1 (PE group), respectively 3 (controls) recordings were considered invalid.

[‡] 1 *nocturnal* recording in the control group was considered invalid.

Abbreviations are: BP, blood pressure, ABP, ambulatory blood pressure.

Values are in mm Hg unless specified otherwise.

Data are expressed in mean ± standard deviation or percentage (absolute) and analyzed using the Kruskall-Wallis test.