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COMMENT

Nocturnal hypertension—solving the puzzle of preeclampsia risk

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Preeclampsia is a complex syndrome complicated by various progressive disorders, such as hypertension, proteinuria, and end-organ dysfunction. Eclampsia is the development of seizures with severe preeclampsia. Preeclampsia/eclampsia (PE) is associated with an increased risk for serious morbidity and mortality in both mothers and neonates. In addition, several studies have reported that patients with PE have an increased risk of cardiovascular disease even over the long term [1].

There are several known risk factors for the development of PE. A previous meta-analysis of 92 cohort studies found that the most significant risk factor was prior preeclampsia and that the second most significant was chronic hypertension [2]. Chronic hypertension is conventionally defined as an office blood pressure (BP) of ≥140/90 mmHg [3]. However, a BP guideline recently published in the US lowered the threshold for the definition of hypertension to ≥130/80 mmHg in office BP for nonpregnant patients [4]. Several studies suggest that this new definition may also be acceptable for pregnant patients. For example, Wu et al. reported that those with stage 1a (130–134 mmHg in systolic BP and/or 80–84 mmHg in diastolic BP) or stage 1b hypertension (135–139 mmHg in systolic BP and/or 85–89 mmHg in diastolic BP) diagnosed in early gestation had significantly increased incidences of hypertensive disorders in pregnancy, including PE, compared to normotensive women (adjusted odds ratio, 2.34 [95% confidence interval, 2.16–2.53]; 3.05 [2.78–3.34], respectively) [5].

Several international BP guidelines recommend the assessment of out-of-office BP for the management of hypertension in nonpregnant patients, but the association between out-of-office BP and the risk of PE has not been widely studied [4]. Salazar et al. [6] investigated the association between out-of-office BP assessed by ambulatory BP monitoring (ABPM) and the risk of the development of late- or early-onset PE in a group of 477 high-risk pregnant women, which included women with prevalent hypertension, diabetes, collagen diseases or antiphospholipid syndrome and chronic renal diseases. Among these 477 individuals, 69 and 44 patients developed late- and early-onset PE, respectively. The patients with nocturnal hypertension (≥120/70 mmHg) had a risk of early-onset PE after adjustment for covariates including daytime BP (adjusted odds ratio, 5.26 [95% confidence interval, 1.67–16.60]) but not a risk of late-onset PE, while these associations were not observed in patients with daytime hypertension. Although the prevalence of early-onset PE is lower than that of late-onset PE, early-onset PE results in more adverse birth outcomes (such as very low birthweight and perinatal death) than late-onset PE. Therefore, the results of the study published by Salazar et al. provide an important strategy for the prevention of early-onset PE. However, in that study, it was not clear why nocturnal hypertension showed a greater association with PE risk than daytime hypertension. It has been proposed that soluble fms-like tyrosine kinase-1 (sFlt-1) secreted from a pathological placenta is strongly linked with the development of PE. sFlt-1 binds vascular endothelial growth factor and placental growth factor, and both of these binding events are known to lead to vascular inflammation, endothelial dysfunction and vascular injury. On the other hand, sFlt-1 is known to be associated with the presence of coronary artery disease and its severity in the nonpregnant population [7]. A previous study reported that the sFlt-1 level was also associated with brain natriuretic peptide (BNP) in ambulatory patients [8]. BNP is produced by cardiac tissue in response to volume overload. Although the mechanism underlying the association between sFlt-1 and BNP is not clear, it has been proposed to involve a direct effect of sFlt-1 on myocardial structure and function.

Increased nighttime BP is associated with a risk of cardiovascular events in both the general and hypertensive populations. In the Japan Morning Surge-Home Blood Pressure (J-HOP) study, which is a prospective observational study exploring the association between home BP and cardiovascular events, both N-terminal-proBNP (NT-proBNP) and nighttime BP assessed by home BP monitoring were associated with cardiovascular events, and nighttime home BP mediated the

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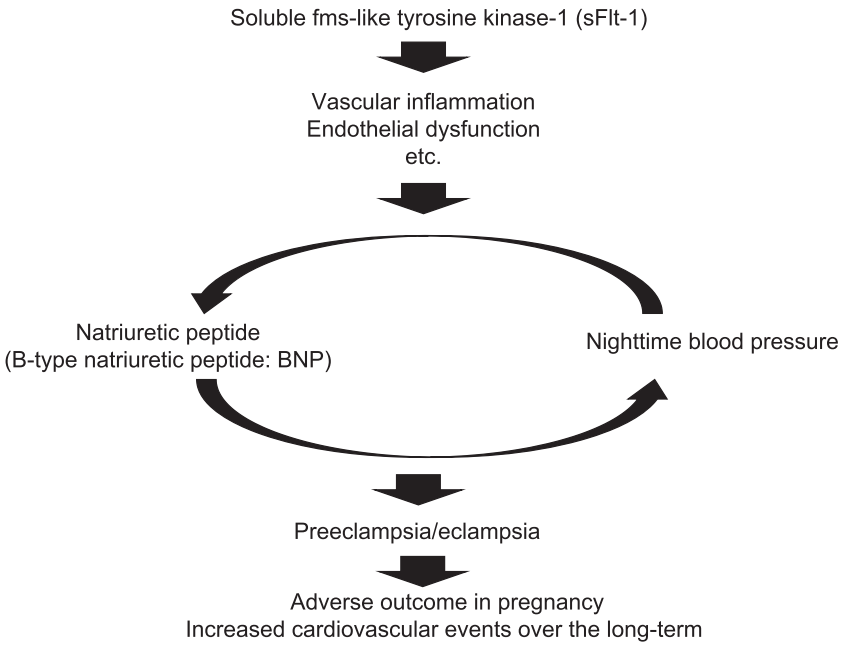

Fig. 1 Association of nighttime blood pressure with preeclampsia/eclampsia

association between elevated NT-proBNP and cardiovascular events [9]. Thus, an increase in NT-proBNP may result in the development of cardiovascular disease via an increase in nighttime BP. The burden of increased nighttime BP, by itself, results in cardiac and renal damage, which may lead to volume overload. In the presence of a pathological placenta, sFlt-1 may produce increased BNP, resulting in an increase in BP, particularly nighttime BP. The results of Salazar et al. may support such an association (Fig. 1).

Nighttime BP measurement is readily performed in clinical practice because ABPM, the gold-standard method for nighttime BP measurement, is relatively convenient and does not disturb sleep. In addition, a more convenient and comfortable validated device for nighttime BP measurement was recently developed [10]. In the future, this improved device may be used to gather evidence on the clinical implications of nighttime BP in pregnancy.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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