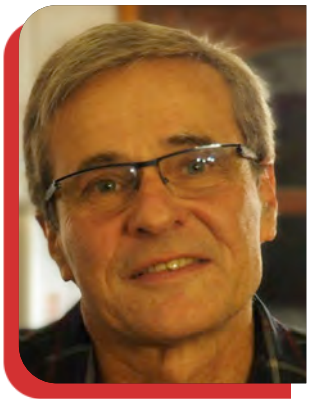
PERSPECTIVES IN HYPERTENSION

Nocturnal hypertension in pregnant women, cause or consequence of placental ischemia?



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The first observation linking elevated nocturnal blood pressure (BP) with preeclampsia (PE) was reported by Redman et al. in Oxford in 1976.[1] In a small cohort of hypertensive pregnant women, they described a reversal of the normal diurnal BP pattern in those with PE, with peak arterial pressure occurring at night. In contrast, women with uncomplicated essential hypertension retained a normal circadian BP rhythm.

Two decades later, Brown et al.[2] conducted a landmark study of 158 women with hypertensive disorders of pregnancy. They demonstrated that nocturnal hypertension was common in these women and – remarkably – was more prevalent in those who developed PE (79% vs. 45%, $p < 0.001$). Moreover, nocturnal hypertension (NH) was strongly associated with adverse maternal and fetal outcomes, including renal insufficiency, liver dysfunction, thrombocytopenia, and low birth weight.

In 2016, we published our first report on the association between nocturnal hypertension and PE.[3] In nearly normotensive and hypertensive pregnant 90 women (mean age ~29 years, mean gestational age ~30 weeks), nocturnal hypertension – defined as BP >120/70 mmHg during the night – was present in 42.5% of participants. Importantly, 27% of these women had normal 24-hour BP values on ambulatory monitoring, revealing a distinct phenotype of isolated nocturnal hypertension. In this study, nocturnal hypertension, whether isolated or combined with daytime hypertension, markedly increased the risk of PE. The risk for isolated nocturnal hypertension was almost fivefold higher (adjusted OR 4.72, 95% CI 1.25–19.43). Moreover, when analyzed as continuous variables, nighttime systolic and diastolic BP levels emerged as the strongest predictors of PE.

The risk of PE rises further when nocturnal hypertension coexists with elevated serum uric acid (SUA). In a recently published study including ~500 women without pre-existing renal disease,[4] participants were stratified into four groups according to nocturnal BP and SUA levels (high SUA was defined by the top quartile: >4 mg/dL): (1) normal SUA + nocturnal normotension, (2) high SUA + nocturnal normotension, (3) normal SUA + nocturnal hypertension, and (4) high SUA + nocturnal hypertension. The absolute risk of PE increased progressively across these groups: 6.5%, 13.1%, 31.2%, and 47.9%, respectively. These findings suggest a synergistic effect between nocturnal BP elevation and hyperuricemia; women with both abnormalities (nocturnal BP >120/70 mmHg and SUA >4 mg/dL) had an extremely high risk of PE (adjusted OR 13.11, 95% CI 6.69–25.70).

PE is a heterogeneous disorder. Early-onset PE (before 34 weeks) is the most severe phenotype and is primarily driven by impaired placental perfusion, whereas late-onset PE is more

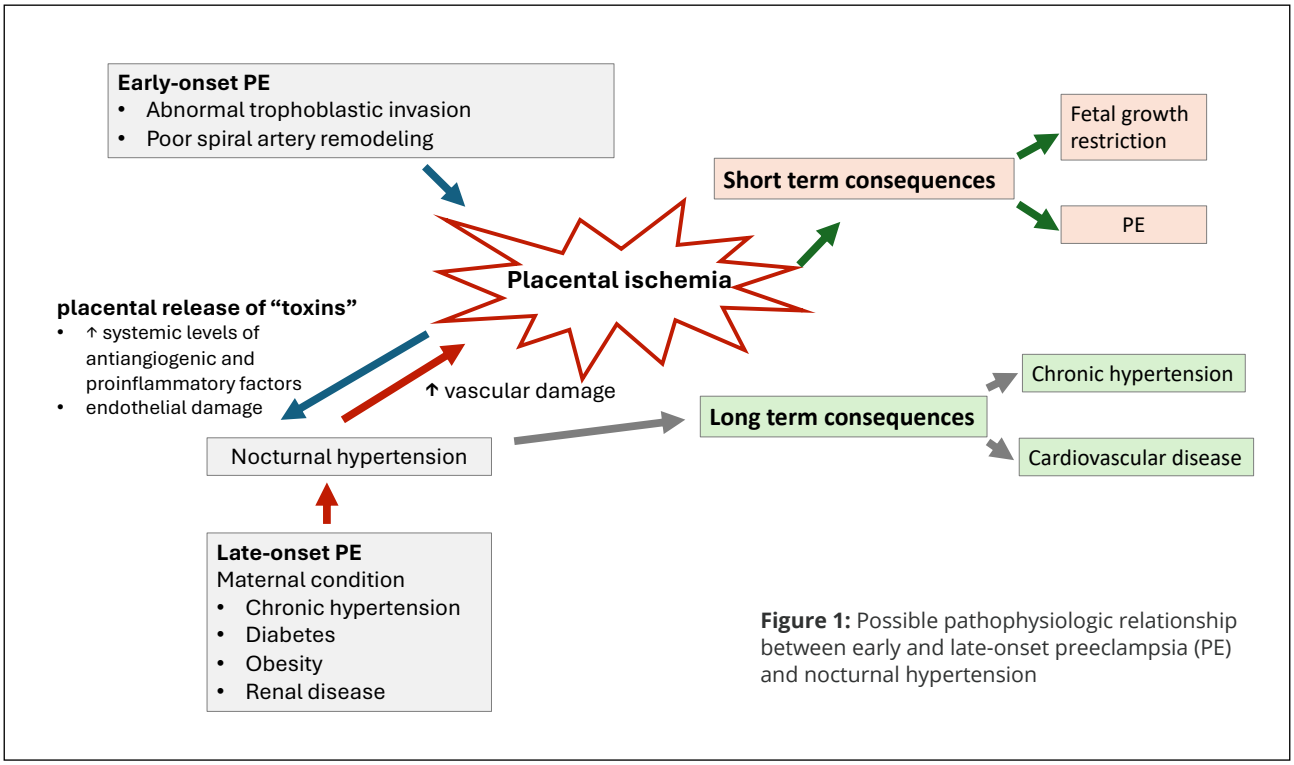

Figure 1: Possible pathophysiologic relationship between early and late-onset preeclampsia (PE) and nocturnal hypertension

closely related to maternal comorbidities such as hypertension, diabetes, and obesity.[5] In a cohort of 477 high-risk pregnancies, we found that nearly 90% of women who developed early-onset PE had nocturnal hypertension.[6] Conversely, early-onset PE was rare in women with normal nocturnal BP (<2%). Nocturnal hypertension was a stronger predictor of early- than of late-onset PE (adjusted OR 5.26, 95% CI 1.67–16.60 vs. 2.06, 95% CI 1.26–4.55). Strikingly, elevated nighttime BP often preceded the clinical onset of PE by several weeks, and in adjusted models, nocturnal – but not daytime – hypertension independently predicted early-onset PE.

Because gestation involves dynamic hemodynamic changes, the relationship between nocturnal hypertension and PE may vary by gestational age. To explore this, we performed ambulatory BP monitoring in 1,363 high-risk pregnant women (mean age ~30 years) at 12–19, 20–27, and 28–36 weeks.[7] The prevalence of isolated nocturnal hypertension increased during the second half of pregnancy, when it became a strong predictor of PE and preterm PE (adjusted OR 3.25, 95% CI 1.95–5.41, and 5.11, 95% CI 3.38–7.97, for 20–27 and 28–36 weeks of gestation, respectively). Before 20 weeks, however, nocturnal hypertension predicted PE only when combined with daytime hypertension (sustained hypertension). These findings suggest that in early gestation nocturnal hypertension may reflect underlying maternal vascular conditions, while later it often emerges as an isolated phenotype, likely reflecting placental dysfunction.

Hypertensive disorders of pregnancy are now recognized as independent risk factors for long-term cardiovascular disease, particularly early-onset PE. In a 30-year follow-up study, cumulative cardiovascular survival was 85.9% in women with early-onset PE, compared with 98.3% in those with late-onset PE and 99.3% in unaffected women.[8] The risk of cardiovascular death was especially elevated among women with PE onset ≤34 weeks. Nocturnal hypertension may help explain this association. In a study of 200 women with prior severe PE assessed by ABPM one year postpartum, Benschop et al. found that 41.5% had hypertension, with nocturnal hypertension being the most prevalent abnormality.[9]

Traditionally, hypertension has been regarded as a cause of vascular injury. Maternal conditions linked to PE – chronic hypertension, diabetes, obesity, renal disease – are often associated with nocturnal

hypertension and may contribute to placental senescence and ischemia, mechanisms most relevant to late-onset PE. By contrast, early-onset PE stems from abnormal trophoblastic invasion and defective spiral artery remodeling, leading to placental ischemia. The ischemic placenta releases antiangiogenic and proinflammatory factors into the maternal circulation, which drive endothelial dysfunction, elevated nighttime BP, and increased SUA levels. Supporting this mechanism, Bouchlariotou et al.[10] showed that nocturnal hypertension in PE was associated with elevated von Willebrand factor (vWF) and soluble adhesion molecules, both markers of endothelial injury.

In conclusion, the relationship between nocturnal hypertension and placental ischemia is likely bidirectional. In early pregnancy, nocturnal hypertension may reflect pre-existing maternal conditions and typically coexists with daytime BP elevation. After 20 weeks, however, isolated nocturnal hypertension often emerges as an early high-risk marker, potentially reflecting systemic endothelial dysfunction driven by placental ischemia. This dysfunction can persist postpartum and carries not only short-term risks (PE, fetal growth restriction) but also long-term implications for maternal cardiovascular health (**Figure 1**).

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