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COMMENT

Dementia: a looming threat for women with hypertensive disorders of pregnancy?

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Hypertensive disorders of pregnancy (HDP) are major causes of maternal morbidity and mortality, contributing to approximately 14% of maternal deaths worldwide. This spectrum includes gestational hypertension, preeclampsia (PE), chronic hypertension (CH), and superimposed PE on CH. These conditions entail both short- and long-term adverse effects on the cerebrovascular health of mothers that persist into their later lives. Patients with HDP exhibit 1.9 and 1.3 times greater hazard ratios (HRs) for coronary heart disease and stroke, respectively, compared to those with a normotensive pregnancy [1]. Dementia is one of the leading causes of death worldwide and has a disproportionate impact on women's life expectancy and quality of life. Over the last decade, the association between HDP and a higher risk of dementia has garnered increasing attention. A study involving over 2000 women [2] demonstrated that those with any history of HDP exhibited impaired cognition, including a significant decline in global cognition and attention/executive function within five years of follow-up, in contrast to those with normotensive pregnancies.

A meta-analysis conducted by Schliep et al. [3] revealed that women with a history of HDP exhibited approximately three times higher risk of vascular dementia and 1.5 times higher risk of Alzheimer's disease, compared to women with normotensive pregnancies. This meta-analysis included both cohort and case-control studies, the outcomes of which were the incidence of dementia, cognitive impairment, and deaths from dementia. Recently, Arafa et al. [4] corroborated these findings with an updated meta-analysis that specifically focused on longitudinal cohort studies on dementia. They demonstrated 1.66 and 1.29-fold higher hazard ratios for vascular dementia and Alzheimer's disease, respectively, with the link between HDP and Alzheimer's disease being marginally significant. Notably, the association between HDP and a higher risk for vascular dementia over Alzheimer's disease aligns with previous research [3, 5, 6]. Although Alzheimer's disease is the most common cause of dementia, most affected patients also exhibit other causes of dementia. Conversely, approximately 90% of the patients diagnosed with vascular dementia show both cerebrovascular disease and Alzheimer's-related brain changes [7]. Despite the prevalence of mixed dementia, none of the studies included in this meta-analysis [4] specifically investigated the correlation between HDP and mixed dementia.

Although evidence is accumulating, a consensus regarding whether and how HDP cause pathological changes in brain structure and function later in women's lives and the mechanisms involved remains elusive. Among the various HDP, PE, a multisystem disorder characterized by the sudden onset of hypertension after 20 weeks' gestation, coupled with at least one end-organ disease, may play a pivotal role in the connection between HDP and dementia. PE is characterized by systemic endothelial dysfunction and inflammation, which adversely affect cerebrovascular health. It is recognized as a risk factor for stroke by the American Heart Association and the American Stroke Association [8]. Several studies have shown significant associations between PE and the risk of vascular dementia, which persist even after adjusting for baseline cardiovascular risk factors and conditions [5, 6]. Neuroimaging studies have revealed that women with a history of PE exhibit increased white matter lesions (a marker of small vessel disease) and gray matter atrophy, compared to those without a history of PE [9]. Additionally, PE contributes to increased central arterial stiffness and pressure, affecting target organs more significantly than the peripheral arteries.

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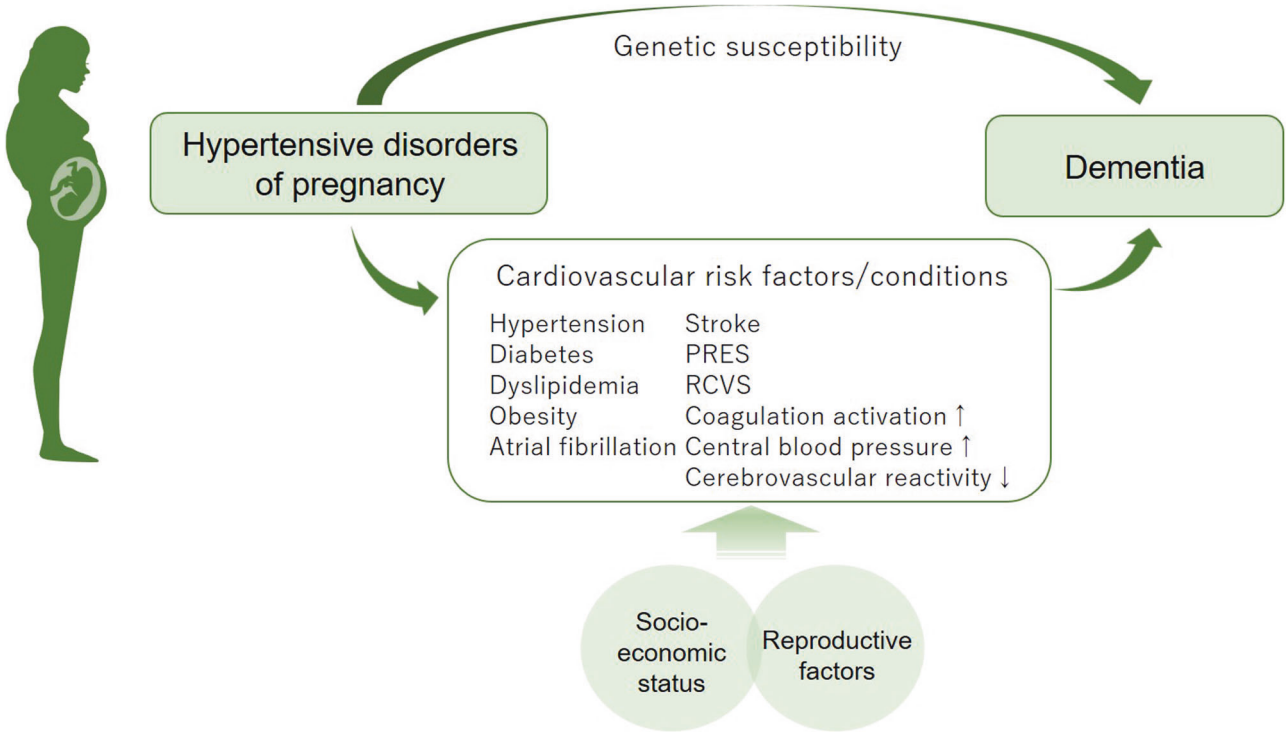
Graphical Opinion



PE can also lead to decreased cerebrovascular reactivity, enhanced coagulation activation, atrial fibrillation, blood brain barrier leakage, posterior reversible encephalopathy syndrome (PRES), and reversible cerebral vasoconstriction syndrome (RCVS), all of which may predispose women to cognitive decline and subsequent dementia.

Possible causal pathways between HDP, particularly PE, and dementia include both direct and indirect pathways (Fig. 1). Although evidence supporting a direct pathway is limited, a Mendelian randomization study [9] suggested a causal relationship between PE and reduced brain volume using PE-associated single nucleotide polymorphisms. Moreover, a recent study highlighted the elevated levels of *cis* P-tau, an early etiological driver and biomarker of Alzheimer's disease, in the blood and placenta of patients with PE. This finding implied that PE shares proteinopathy-associated features [10]. Meanwhile, indirect effects of HDP on cardiovascular risk factors and conditions are also important. Specifically, the link between HDP and dementia mediated by stroke, a risk factor that can be intensified via the aforementioned mechanism, significantly contributes to the indirect pathway. Previous studies have shown that HDP exhibits a stronger correlation with vascular dementia than with Alzheimer's disease, which may be partly attributed to this indirect pathway.

As highlighted by Arafa et al. [4], previous studies employing mediation analyses revealed that more than 60% of the correlation between HDP and dementia was mediated by cardiovascular risk factors and conditions that manifest in women after pregnancy [1, 5]. This finding indicates that the seamless follow-up of women with a prior history of HDP is crucial to prevent possible adverse outcomes. Dayan et al. [11] indicated that adjusting for cardiovascular risk factors attenuated the association between HDP and a higher risk of dementia. Previous research has also highlighted the influence of socioeconomic status, reproductive factors (potentially influenced by socioeconomic status), and genetic susceptibility on the association between HDP and dementia [2, 11, 12]. The correlation between HDP and dementia appears to be multifaceted and intertwined with these diverse factors.

Although HDP also encompass masked hypertension as a form of CH diagnosed before 20 weeks' gestation [13], evidence of its association with postdelivery dementia remains scarce. A recent retrospective cohort study indicated that the percentage of PE with severe features in pregnant women with masked hypertension was ten times higher than that in pregnant women without masked hypertension [14]. It is estimated that approximately one in four high-risk pregnant women (for example, those with diabetes, chronic kidney disease, or multiple pregnancies) is diagnosed with masked hypertension [15]. Considering the increasing prevalence of high-risk pregnancies worldwide, it is imperative to identify undiagnosed masked

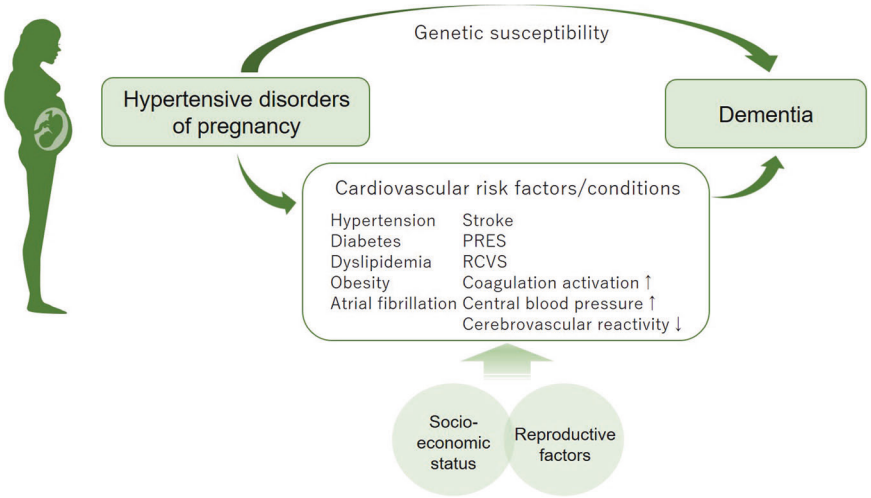


Fig. 1 Possible causal pathways between hypertensive disorders of pregnancy and dementia

hypertension in pregnant women, which may make them "masked" patients with latent susceptibility to dementia, through blood pressure monitoring at home.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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