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COMMENT

Placental hypoxia, high nighttime blood pressure, and maternal health

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Hypertension disorders during pregnancy (HDP) have a wide range of severities, from clinical conditions with mild or no consequence for the mother and fetus, to life-threatening ones, with the development of preeclampsia and eclampsia as the main complication (PE). PE is the leading cause of neonatal and maternal morbidity and mortality worldwide [1]. Office blood pressure (BP) and proteinuria have traditionally been used to identify PE. However, clinical hypertension and overt proteinuria are late manifestations of a physiopathological chain of events initiated for placental ischemia, being fetal growth restriction and a systemic inflammatory state in the mother with multiorgan damage the main consequences. Identifying these women with high risk of poor maternal and neonatal outcomes is an essential but challenging clinical task and different approaches have been proposed in the last years.

One of these approaches is based on the disbalance between angiogenic and antiangiogenic placental factors characteristic of PE. In normal pregnancy, appropriate extravillous trophoblast invasion in the maternal endometrium leads to a sufficient maternal blood flow from the spiral artery. The placental growth factor (PlGF), which is secreted from the placenta, activates the vascular endothelial growth factor (VEGF) and maintains a healthy endothelium. On the other hand, PE begins with abnormal trophoblast invasion and spiral artery remodeling before clinical manifestations of the disease become apparent. Incomplete invasion of the extravillous trophoblast leads to insufficient maternal blood flow from the spiral artery and subsequent placental hypoxia. Soluble fms-like tyrosine kinase-1 (sFlt1) is secreted from the placenta, which suppresses VEGF resulting in systemic endothelial dysfunction [2]. The sFlt-1/PlGF ratio has been widely used to exclude preeclampsia within 7–14 days because both have good negative predictive value for up to 4 weeks. However, the positive predictive value is low [3].

Another approach proposes the use of ambulatory blood pressure monitoring (ABPM) in order to detect early changes in BP comportment in women who will subsequently develop PE. Previously published studies performed in high-risk pregnancies using ABPM showed that adjusted relative risks increased ~5 times with the presence of nocturnal hypertension and ~8 times with masked hypertension; both conditions that cannot be detected using only office readings. Remarkably, nocturnal systolic BP and diastolic BP had the highest abilities to predict PE, especially the early-onset variant [4, 5]. Interestingly, nocturnal hypertension precedes some weeks the development of clinically overt disease. Moreover, masked hypertension increases the risk of poor neonatal outcomes [6].

In an interesting study published in this number of Hypertension Research, Chen et al. [7] showed that sFlt-1/PlGF ratio is correlated with both, nocturnal BP and a non-dipper pattern. The authors conducted an observational study in 476 women who had one of the suspicious symptoms of PE but did not reach the diagnosis criteria. The sample was divided according to sFlt-1/PlGF ratio using a value of 38 as the cut point. Women with high sFlt-1/PlGF had higher daytime and nighttime BP values and a higher prevalence of non-dipper pattern (58.4% vs. 46 30.3%). Moreover, sFlt-1 was positively correlated with systolic and diastolic daytime and nighttime BP, but PlGF was only negatively associated with nighttime BP. The correlation coefficient of sFlt-1 was higher for nighttime BP than for daytime BP. Evaluated using AUC, the combination of both approaches (ABPM plus serum sFlt-1/PlGF ratio) improved the ability to predict PE compared to the

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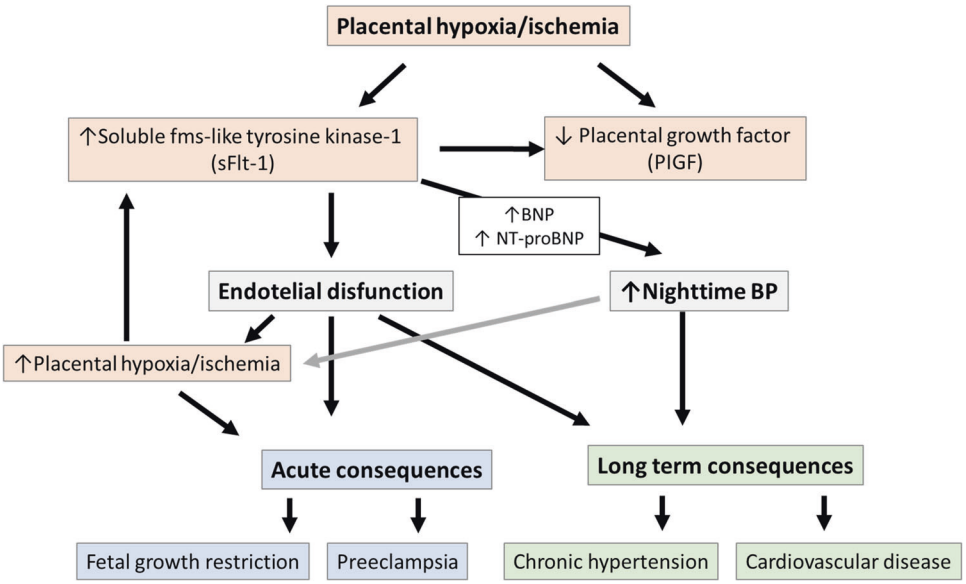

Fig. 1 Relationships between placental hypoxia/ischemia, nighttime blood pressure, preeclampsia, and cardiovascular disease. BP blood pressure

ABPM or sFlt-1/PlGF ratio alone, particularly yielding higher positive predictive values.

Although undoubtedly valuable, some important limitations should be pointed out. This is a single-center study including only Asian population. Moreover, the inclusion criteria (suspicious symptoms of PE) produced a selection bias identifying pregnancies at very high risk for PE. Indeed ~30% of the women developed PE in the follow-up period. Thus, the findings would not be necessarily applicable to women with normal pregnancies or belonging to other ethnic groups. However, despite this limitation, and beyond the potential clinical applications, this study highlights the relationships between placental disease and changes in the maternal patterns of BP.

The pathophysiological mechanisms involved in the relationship between placental ischemia, nocturnal hypertension, and cardiovascular disease are not completely understood. Several deleterious cardiovascular and renal effects of the imbalance between antiangiogenic and angiogenic placental factors have been previously described. The signaling system of the vascular endothelial cell growth factor (VEGF) family consists of five ligands (VEGF-A, PlGF, VEGF-B, VEGF-C, and VEGF-D) and three tyrosine kinase receptors (Flt-1 Flk-1, and Flt-4). Also, Flt-1 has a soluble isoform (sFlt-1). Although originally discovered in the human placenta, this signaling system is abundantly expressed in endothelial cells and plays various roles in inflammatory diseases, including atherosclerosis [8]. sFlt-1 is to be associated with the presence of coronary artery disease in the nonpregnant population. Furthermore, previously published studies showed that higher plasma levels of sFlt-1 in the acute phase of acute myocardial infarction are associated with acute severe heart failure (HF). Moreover, plasma levels of sFlt-1 are higher in patients with chronic HF and positively correlated with both, plasma BNP levels and HF severity [8]. In cases of placental hypoxia, trophoblasts produce massive amounts of sFlt-1 that circulates systemically in the mother leading to endothelial dysfunction, hypertension, and proteinuria.

On the other hand, nocturnal hypertension is a strong predictor of cardiovascular morbidity and mortality. Previously published studies showed that nighttime BP is more predictive of adverse outcomes than daytime or even 24-h BP. Patients with nocturnal hypertension are more likely to develop cardiac and carotid structural changes than people with nocturnal normotension. Moreover, isolated nocturnal hypertension (nocturnal hypertension in people with normal office BP and normal daytime BP) is associated with hypertension-mediated organ damage and adverse outcomes. In non-pregnant individuals, different mechanisms can lead to nocturnal hypertension, including increased SNS activity, autonomic dysfunction, impaired baroreflex sensitivity, salt sensitivity, increased plasma volume, RAS hyperactivity, OSA and other sleep disturbances, increased stress and renal dysfunction [9]. In the Japan Morning Surge-Home Blood Pressure (JHOP) study, both N-terminal-proBNP (NT-proBNP) and nighttime BP were associated with cardiovascular events, suggesting a physiopathological pathway in which increased nighttime BP contributes to the impact of high NT-proBNP levels on cardiovascular disease [10]. A previously published study performed in ambulatory high-risk patients reported that the sFlt-1 level was also associated with high brain natriuretic peptides (BNP) in ambulatory high-risk patients [11]. Thus, an elevated BNP could be a link to explain the association sFlt-1 and high nighttime BP observed by Chen et al. [7].

Maternal consequences of placental ischemia are not limited to acute events such as the development of PE,

placental abruption, stroke, pulmonary edema, thromboembolic events, multiple organ failure, and disseminated intravascular coagulation. Adverse outcomes of pregnancy are now recognized as strong risk factors for future cardiovascular disease. Women with antecedents of HDP are at an increased risk for developing future sustained hypertension and cardiovascular events [9]. Furthermore, the antecedent of PE markedly increases the risk of coronary arterial disease, heart failure, and stroke as soon as 1 year after the index pregnancy. There is a direct relationship between the severity of the PE and the level of future risk [12].

Thus, we can hypothesize a chain of short-term and long-term maternal pathological events triggered by placental ischemia (Fig. 1). The systemic increase of sFlt-1 could produce vascular damage and daytime nocturnal hypertension. This could result in more placental ischemia and trigger a sequence of acute events with fetal growth restriction and PE, eclampsia, or HELP. Moreover, the study by Chen et al. showed that the serum PlGF level was negatively correlated with nighttime BP but had no correlation with daytime BP, suggesting a specific interaction between PIGF and nighttime BP [7]. After delivery, nocturnal hypertension and some degree of vascular damage could persist, leading to short- and long-term increases in cardiovascular risk [12].

In conclusion, although reasonable, the utility of the combined approach (sFlt-1/PlGF ratio plus ABPM) to predict PE should be confirmed with studies including women with lower risk, and of other ethnic groups. However, although the intimal mechanisms remain to be elucidated, the study by Chan et al. strongly supports the role of high nighttime BP as an important link between placental ischemia and both, the development of PE and the increase in the maternal risk of coronary arterial disease, stroke, and heart failure observed in these women.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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