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Mitigating pre-eclampsia risk: an integrated approach

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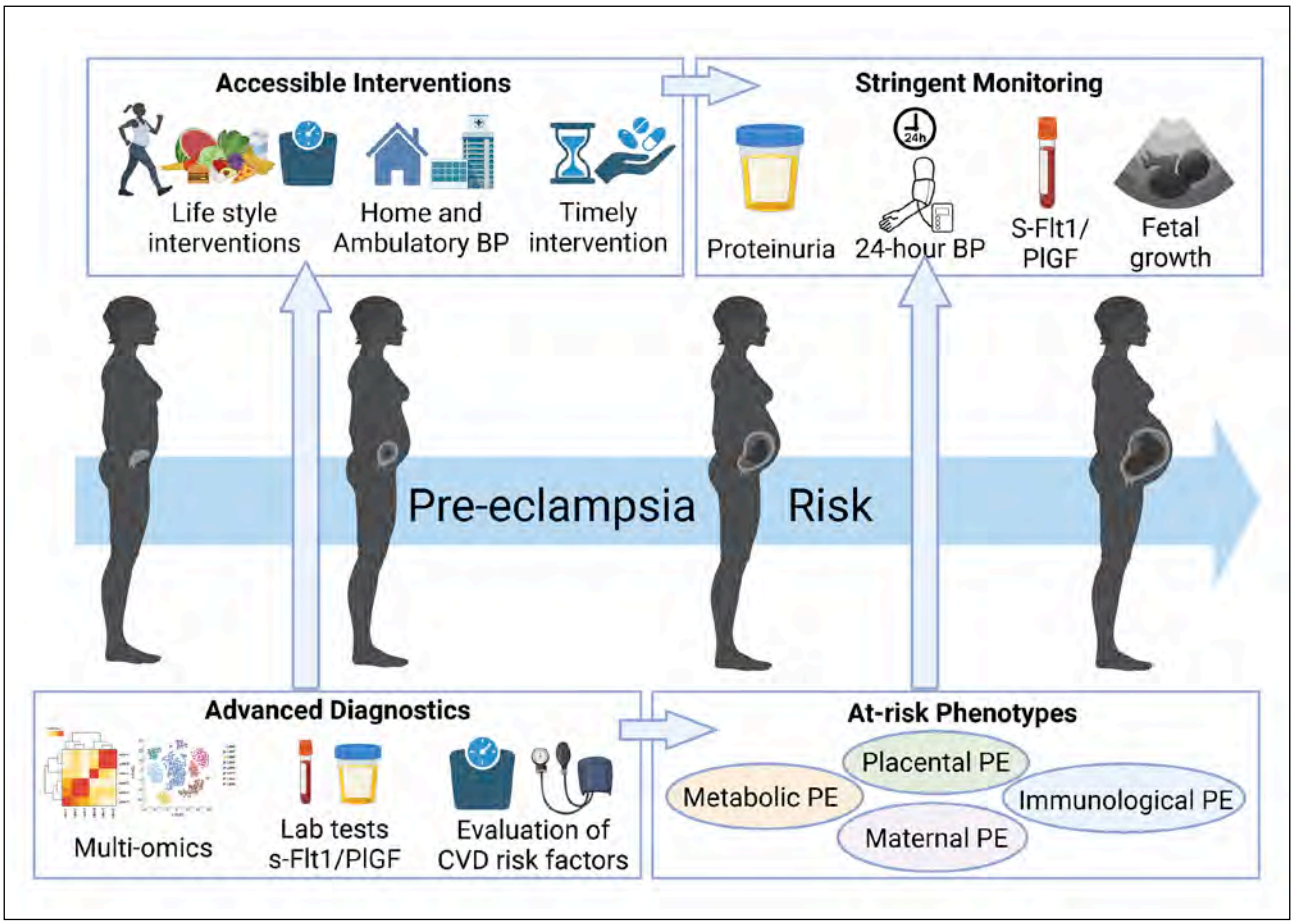
Pre-eclampsia is a complex hypertensive disorder of pregnancy with significant risks to maternal and fetal health. It is the second leading cause of maternal morbidity and mortality worldwide[1] and is associated with adverse fetal outcomes, including preterm birth and intrauterine growth restriction.[2, 3] The pathogenesis of pre-eclampsia involves complex interactions between the placenta, maternal vascular endothelium, and immune system.[4,5] Endothelial dysfunction is central to its development, characterized by impaired remodeling and reduced dilation of uterine arteries, compromising placental perfusion and triggering an exaggerated inflammatory response.[4,6] These disruptions often arise from abnormal placentation, where defective trophoblast invasion leads to insufficient remodeling of the uterine spiral arteries and placental ischemia. However, maternal factors such as cardiometabolic conditions and advanced maternal age can also contribute to impaired vascular function, exacerbating the risk of pre-eclampsia by hindering placental vascular development.[7] Effective risk mitigation therefore requires a deep understanding of this complex pathogenesis, an early identification of high-risk pregnancies, and personalized preventive strategies.

Placental ischemia induces the release of antiangiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, which disrupt the balance with proangiogenic molecules such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).[8] This imbalance leads to widespread endothelial damage, systemic inflammation, and multi-organ dysfunction, including renal, hepatic, and neurological complications. Fetal growth restriction also commonly occurs due to compromised uteroplacental blood flow. Although these features are commonly present in most cases of pre-eclampsia, individual factors may also interplay with these or other mechanisms, adding complexity to its pathogenesis and influencing its clinical manifestations. This heterogeneity poses a significant challenge in discovering new treatments and reduces the effectiveness of current therapeutic options for managing hypertensive disorders of pregnancy in general. Taking this into account, the following critical points described below and illustrated in **Figure 1** must be considered in the pursuit of strategies to effectively mitigate pre-eclampsia risk.

Identification of individuals at-risk

Pre-eclampsia is highly heterogeneous, presenting various clinical phenotypes based on onset (early or late), severity, and associated complications. Risk factors include chronic hypertension, obesity, diabetes, autoimmune diseases, advanced maternal age, and certain genetic predispositions. The phenotypes reflect a combination of maternal characteristics, placental pathology, and environmental factors. Identifying these phenotypes early allows better risk prediction and tailored preventive interventions. For example, women with a history of pre-eclampsia may benefit from closer surveillance, while those with a metabolic phenotype (e.g., obesity or insulin resistance) might benefit from lifestyle modifications alongside pharmacological support. These stratified approaches could ensure that treatment aligns with individual risk profiles, enhancing prevention and outcomes.

Figure 1: Integrated strategies for understanding and mitigating pre-eclampsia risk. BP, blood pressure; CVD, cardiovascular disease; PE, pre-eclampsia; PlGF, placental growth factor; s-Flt1, soluble fms-like tyrosine kinase-1.



Additionally, advances in systems medicine have opened new opportunities for understanding these different phenotypes and mitigating pre-eclampsia. By integrating clinical data with multi-omics insights, researchers can identify biomarkers and molecular signatures linked to increased risk.[9] For example, altered levels of sFlt-1 and PlGF are early predictors of pre-eclampsia, enabling timely diagnosis and intervention.[10] Systems medicine also supports personalized strategies, with multi-omics data and machine learning algorithms uncovering patient-specific risk patterns for more precise interventions.[9,11] This approach underscores the potential of precision medicine to transform the prediction and management of hypertensive disorders of pregnancy.

Accessible interventions

Mitigating pre-eclampsia risk requires both advanced diagnostics and accessible interventions that can be implemented widely. While biomarker-based tools and predictive models are essential, simple and practical measures can significantly reduce risks at the population level. Encouraging pregnant women to monitor their blood pressure at home or undergo periodic ambulatory monitoring can facilitate early detection of hypertensive changes. Although the BUMP1 randomized controlled trial did not show significantly earlier detection of hypertension with self-monitoring during pregnancy,[12] this approach empowered women by increasing awareness of raised blood pressure.[13] This underscores the importance of pairing self-monitoring with timely medical intervention, as highlighted in the POP-HT study, which demonstrated better postnatal outcomes when prompt intervention followed blood pressure changes.[14] Thus, a combination of closer monitoring and timely medical response and intervention during pregnancy may prove more effective in preventing pre-eclampsia. Additionally, lifestyle interventions including balanced nutrition, regular physical activity, and

weight management are crucial, particularly for women with metabolic risk factors.[15,16] Programs that promote healthy eating and exercise should be initiated early in pregnancy, especially for women with cardiovascular risk factors or advanced age, as they may substantially reduce the likelihood of developing pre-eclampsia.

Stringent blood pressure and abnormalities monitoring:

Recent studies have also emphasized the importance of treating mild chronic hypertension during pregnancy, demonstrating the value of ambulatory blood pressure monitoring (ABPM) for identifying at-risk groups.[17, 18] Sustained and masked uncontrolled hypertension significantly increase the risk of pre-eclampsia, while controlled or white-coat hypertension do not.[18] Nocturnal hypertension is a particularly strong predictor of pre-eclampsia, underscoring the need for precise blood pressure monitoring. These findings advocate for ABPM to detect masked hypertension and recommend stringent 24-hour monitoring, especially nocturnal blood pressure, to improve diagnosis, management, and prevention. Pharmacologically treated women also need access to regular antenatal visits with screening for proteinuria, blood pressure monitoring, and ultrasonographic evaluation of fetal growth to detect early abnormalities.

In conclusion, pre-eclampsia requires a comprehensive prevention strategy. The combination of precision medicine, systems biology, timely interventions, and community health initiatives offers promising avenues to reduce risks. By leveraging big data and artificial intelligence, healthcare providers can refine risk stratification models and develop tailored therapeutics. However, these measures must be supported by investments in public health infrastructure to enable stringent monitoring, provide accessible lifestyle counseling, and raise awareness among expectant mothers. A holistic strategy, can help ensure safer pregnancies and improved maternal-fetal outcomes.

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