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Review Article

Pre-eclampsia: Molecular events to biomarkers

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ABSTRACT

Pre-eclampsia is a hypertensive disorder in pregnancy, which accounts for 10–15% of the maternal and perinatal mortality worldwide. Abnormal placental development and tissue hypoxia are its main etiologic factors. The present diagnostic methods of blood pressure monitoring and renal function evaluation are insufficient in the early detection of pre-eclampsia. Since molecular events portent well ahead of the disease onset, biomarker research for the early diagnosis of pre-eclampsia has recently generated ambitious clinical targets. However, no clinically validated biomarker has so far been reported for the prediction of pre-eclampsia. Therefore, this review takes stock of the current understanding of pre-eclampsia from a molecular biology perspective and critically evaluates the following diagnostic potentials claimed for the biomarkers: placental proteins, angiogenic markers, and cell-free fetal DNA (cffDNA) in maternal circulation. Though the emerging evidences in favor of the fetal-specific epigenetic marker, hypermethylated RASSF1A of cffDNA, are highlighted, it pitches for a broader strategy of 'combination biomarker approach' for the reliable forecasting and triaging of pre-eclampsia.

Introduction

Hippocrates in 4th century BC described hypertensive disorders of pregnancy as a '*worse state with headache, heaviness and convulsions*.'[1] Based on the etiology and symptoms, it later came to be called as toxemia, gestosis, pregnancy-induced hypertension, or pre-eclampsia. A consensus on the classification and definition of hypertensive disorders of pregnancy emerged in the 12th world congress of International Society for the Study of hypertension (ISSHP) in Paris in 2000. Accordingly, the disease entity has now been categorized as the following: pre-eclampsia/eclampsia, gestational hypertension, chronic

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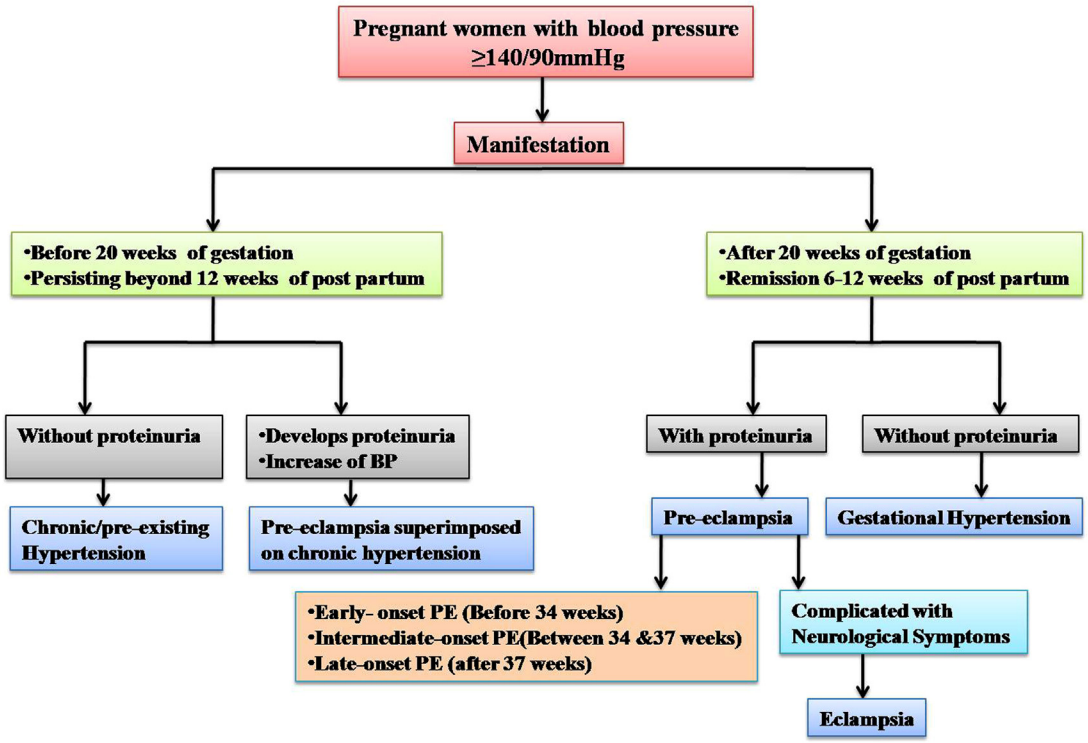

Fig. 1 – Classification of hypertensive disorders.

(pre-existing) hypertension, and pre-eclampsia superimposed on chronic hypertension.[2] The classification of hypertensive disorders is in Fig. 1.

Pre-eclampsia is a hypertensive complication affecting 2–8% of the pregnancies. It is thereby a major contributing factor for the high maternal/perinatal mortality and morbidity seen worldwide.[3] Pre-eclampsia patients with high blood pressure can go to an extreme of HELLP syndrome. Hemolysis with elevated liver enzymes and low platelets and further onset of neurological symptoms lead them to eclampsia. Eclampsia is characterized by the following multiple organ involvement: hepatic/renal failure, disseminated intravascular coagulation, pulmonary/cerebral edema, and hemorrhage. The complications occur not only to the mother but also to the fetus – increased risk of respiratory ailments, intrauterine growth restriction (IUGR), and preterm birth.[4] Maternal and neonatal complications of pre-eclampsia are summarized in Fig. 2.

The risk factors for pre-eclampsia are the following: maternal age over 40 years, obesity, nullipary, family/previous history, renal or autoimmune disorders, and multiple pregnancies. Diagnosis of pre-eclampsia is usually done by determining blood pressure and proteinuria. However, these are insufficient in detecting the disease either in the early presymptomatic stages or in rightly assessing fetal

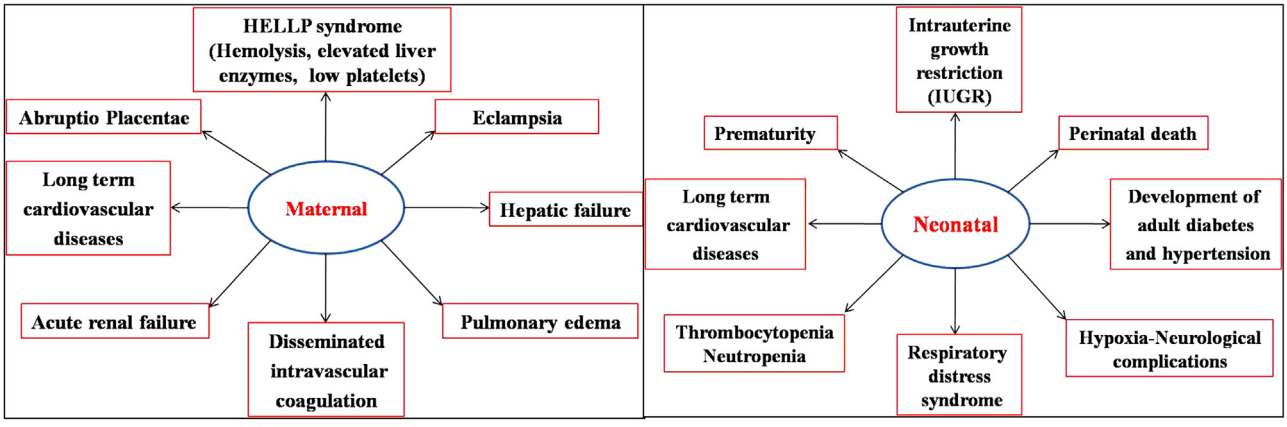

Fig. 2 – Maternal and neonatal complications of pre-eclampsia.

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