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COMMENT

Pentraxin-3 and the pathogenesis of preeclampsia

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Hypertensive disorders of pregnancy are a heterogeneous group of high blood pressure (BP) disorders that include chronic hypertension, gestational hypertension, pre-eclampsia–eclampsia, and other hypertensive effects (white-coat hypertension, masked hypertension, and transient hypertension) [1, 2]. More simply, hypertension in pregnancy may be chronic (predating pregnancy or diagnosed before 20 weeks of pregnancy) or occur de novo (either preeclampsia or gestational hypertension) [1].

Among de novo forms of hypertension, preeclampsia is a multisystem progressive disorder occurring in the last half of pregnancy or postpartum that is characterized by the new onset of hypertension associated with proteinuria or significant target organ dysfunction [1].

Eclampsia (the occurrence of new onset, generalized, tonic-clonic seizures, or coma) and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome are manifestations of preeclampsia [1].

Of note, gestational hypertension may be considered a provisional diagnosis for hypertensive pregnant women who do not meet the criteria for preeclampsia or chronic hypertension. Thus, during pregnancy, the diagnosis may change to preeclampsia, chronic hypertension, or transient hypertension.

Hypertensive disorders of pregnancy complicate ~6–11% of all pregnancies and are associated with adverse maternal and fetal outcomes, particularly when high BP is due to preeclampsia [1]. Moreover, preeclampsia complicates 4.6% of all pregnancies each year, resulting in ~50,000–60,000 deaths annually worldwide [3].

Despite decades of research, preeclampsia remains a complex medical disorder to fully understand. Indeed, preeclampsia is a multisystemic syndrome involving many genetic and environmental factors in its pathogenesis and pathophysiology.

In the last few years, the role of several markers has been tested to elucidate the pathophysiology of preeclampsia; numerous biochemical markers have been identified, including plasminogen activator inhibitor, soluble fms-like tyrosine kinase, placental growth factor, von Willebrand factor, leptin, C-reactive protein, serum uric acid, urinary proteomics, inherited thrombophilia factor V Leiden mutation, protein C or S deficiency, antithrombin III deficiency, antiphospholipid antibodies, α-fetoprotein, human chorionic gonadotrophin, and plasma tumor necrosis factor-α [4]. Of note, experimental models developed to better elucidate the mechanisms involved in the development of placental and maternal vascular dysfunction in preeclamptic women strongly support the pivotal role of oxidative stress and inflammation.

In this context, the results of the Genetics and Pre-Eclampsia (GenPE) study [5] published in the current issue of the journal offer the chance to test the biological plausibility of the role of pentraxin-3 as a novel inflammatory marker in the pathophysiology of this disorder.

Briefly, the GenPE study is a multicenter and case–control study that recruited pregnant women at the time of delivery in eight Colombian cities. Overall, 1024 pregnant women (461 controls, 368 women with pre-eclampsia, and 195 with HELLP syndrome) were included in the analysis. After adjustment for potential confounders (including age, ethnicity, socioeconomic status, smoking status, body mass index, gestational age, and multiple pregnancy), for each unit increase (1 ng/ml) of pentraxin-3 levels, the risk of preeclampsia and HELLP syndrome increased by 6% (odds ratio [OR]: 1.06, 95% confidence

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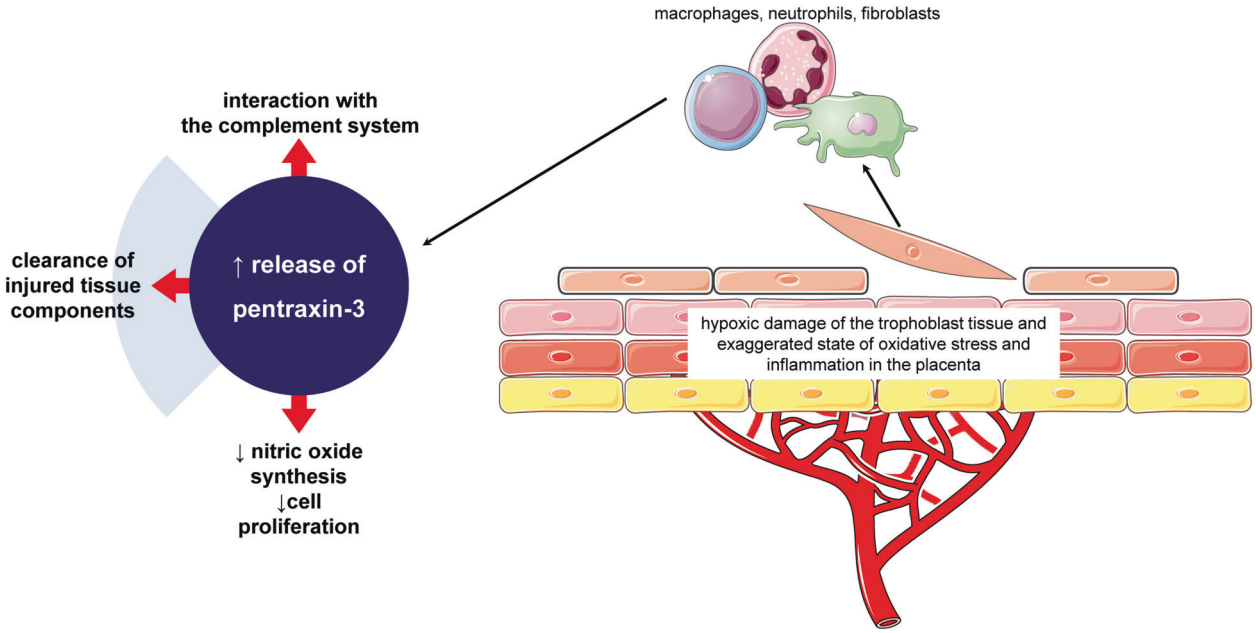

Fig. 1 Effects of pentraxin-3 (left panel) and mechanisms involved in the pathogenesis of preeclampsia (right panel). See text for details

interval [CI]: 1.03–1.10, $p < 0.001$). A similar relationship was found for HELLP syndrome (OR: 1.13, 95% CI: 1.08–1.18, $p < 0.001$).

These findings suggest the potential involvement of pentraxin-3 in the pathogenesis of severe forms of hypertensive disease in pregnancy. Nonetheless, knowledge on the functions of pentraxin-3 and inflammatory adaptations in pregnancy is required to correctly interpret the results.

Pentraxin-3 regulates inflammation, activating and interacting with multiple components of the complement system (classical pathway), and coordinates spatially and temporally targeted clearance of injured tissue components [6].

Although mainly expressed by vascular endothelium and smooth muscle cells, pentraxin-3 is also synthesized by myeloid dendritic cells, macrophages, fibroblasts, adipocytes, synovial cells, and chondrocytes [6]. Of note, within endothelial cells, pentraxin-3 decreases nitric oxide synthesis, inhibits cell proliferation, and alters their function [6] (Fig. 1).

As mentioned above, maternal inflammation seems to be a key factor in the etiology of preeclampsia. More specifically, the fetal trophoblast is regarded as an alloantigen, and the mother reacts to this and mounts a low-grade systemic inflammatory response. To date, it is believed that in preeclamptic compared with normal pregnancies, there is an exaggerated inflammatory response and endothelial dysfunction, resulting in an increased release of inflammatory markers in the circulation (Fig. 1). Moreover, the failure to establish adequate uteroplacental blood flow in preeclamptic women can result in hypoxic damage of the trophoblast tissue, promoting an exaggerated state of oxidative stress and inflammation in the placenta [7].

In this context, the analysis by Colmenares-Mejia et al. [5] confirms the role of inflammation in the pathogenesis of preeclampsia. Specifically, the results suggest that interactions between pentraxin-3 and the complement system are potentially also involved in conditions such as preeclampsia, where tissue damage and necrosis often occur [7] (Fig. 1). Nonetheless, and as stated by the authors [5], the usefulness of pentraxin-3 during pregnancy to stratify the risk for the development of hypertensive disease remains unproven.

In conclusion, epidemiological evidence supporting the worse prognosis associated with hypertensive disorders of pregnancy provides a strong basis for the development of risk prediction models to identify women whose gestations may be considered at high risk [8]. The identification of pregnant women requiring closer surveillance and preventive treatment is the real challenge in this setting.

Unfortunately, the mechanisms involved in the pathogenesis of hypertensive disorders of pregnancy are complex and still largely unknown. In the last few years, multiple potential biomarkers (including pentraxin-3) have been identified [4]. Nonetheless, further studies are still required to provide a better understanding of the key processes in the development of hypertension during pregnancy, and current evidence does not support the use of a single biomarker to predict severe forms of hypertension in pregnancy.

In our opinion, only a combination model including clinical, laboratory, and instrumental examinations (uterine artery Doppler assessment and electrocardiography) may

become a robust predictive model for hypertensive disorders of pregnancy [8–10].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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