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Editorial

Maternal serum markers and preeclampsia

Preeclampsia is a pregnancy related condition identified by hypertension and proteinuria after the 20th week of gestation and complicates 2–8% of pregnancies worldwide, contributing to a major cause of maternal, fetal, and neonatal morbidity and mortality [1]. Although the pathogenesis of preeclampsia is not entirely clear, preeclampsia is thought to develop as a result of abnormal placental implantation (inadequate trophoblast invasion and insufficient spiral artery remodeling), followed by endothelial dysfunction with subsequently resulting vasospasm, coagulopathy, or changes in capillary permeability and inflammatory response; this underscores the importance of successfully established circulation networks between the fetus and mother [2]. These established circulation networks require an ongoing sequential and complicated process—angiogenesis [2]. The only effective treatment for the abatement of preeclampsia symptoms is delivery; therefore recent research has been focused on the identification of specific and sensitive biomarkers for early prediction of preeclampsia, including several angiogenic, antiangiogenic, inflammatory, biophysical (mean arterial pressure and uterine artery Doppler) biomarkers, alone and in combination [3]. However, all of them have been proposed for prediction, but predictive values are limited hindering their use in clinical settings [3]. The lack of mechanistic understanding makes early diagnosis and prevention of preeclampsia nearly impossible [3]; therefore, any biomarker reported to be useful for early diagnosis of preeclampsia is welcome.

The study by Tuten et al [4] in the current issue of the *Taiwanese Journal of Obstetrics and Gynecology* was conducted to investigate the potential biomarker of copeptin as a predictive model of preeclampsia by examining the maternal serum levels of copeptin in pregnant women with and without preeclampsia. The authors found that the mean maternal serum copeptin levels were higher in both early- and late-onset preeclampsia compared with the control groups, and there was a statistically significant difference in early-onset preeclampsia, which was defined as having a preeclampsia before 34 weeks of gestation [4]. Copeptin, a glycopeptide, makes up the C-terminal portion of prepro-arginine vasopressin, which is the precursor protein of vasopressin (AVP), a vasoactive neuropituitary hormone, and acts as a carrier protein for AVP in conjunction with neurophysin II [5]. AVP plays a major role in the regulation of blood pressure and water and maintains homeostasis of electrolytes, suggesting that AVP may involve the pathophysiology of preeclampsia. However, the characteristics of AVP, including the short half-life and instability, make reliable detection nearly impossible [5]. Copeptin is produced in a 1:1 ratio to AVP, has a longer half-life, and is more stable in serum, rendering it a clinically useful biomarker of AVP secretion [5].

A few other studies have tested the association of maternal serum levels of copeptin and occurrence of preeclampsia. Zulfikaroglu et al [6] found that plasma levels of copeptin were 0.31 ± 0.09 ng/mL in the normotensive pregnant group ($n = 32$), 0.62 ± 0.16 ng/mL in the mild preeclamptic group ($n = 32$), and 0.85 ± 0.18 ng/mL in the severe preeclamptic group ($n = 32$; $p < 0.001$), suggesting that increased maternal levels of copeptin might be useful in the assessment of the severity of the disease [6]. Both Foda et al [7] and Santillan et al [8] also supported the above-mentioned findings; that higher maternal serum copeptin levels were found in pregnant women with preeclampsia as compared with normotensive pregnant women. Furthermore, the sequential follow-up study by Santillan et al [8] further showed that copeptin significantly predicted preeclampsia throughout gestation as early as the 6th week of gestation in the first trimester (area under the curve = 0.90, $p < 0.0001$, cutoff = 811, sensitivity = 88%, and specificity = 81%), suggesting that copeptin might be a novel, robust, and clinically useful biomarker for the prediction of preeclampsia in very-early pregnancy [9]. In an animal model, chronic infusion of AVP during pregnancy (24 ng per hour) is sufficient to phenocopy preeclampsia in C57BL/6J mice, causing pregnancy-specific hypertension, renal glomerular endotheliosis, proteinuria, and intrauterine growth restriction [8]. A study by Yeung et al [10], possibly biggest sample-sized study, also confirmed the correlation between copeptin levels and preeclampsia and demonstrated that increased copeptin was specifically predictive to the development of preeclampsia.

Taken together, in the absence of effective treatment of preeclampsia except delivery, the identification of biomarkers for early diagnosis of preeclampsia is of great importance and these new biomarkers, such as proangiogenic placental growth factor, antiangiogenic soluble fms-like tyrosine kinase 1, placental protein 13, pregnancy-associated plasma protein A, copeptin, cystatin C (measure of renal function), leucyl/cystinyl aminopeptidase, vasopressinase, many other microparticles and miRNA [9,11], might help the development of new therapeutic targets that might provide a more effective treatment option for this devastating disease—preeclampsia.

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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