Editorial

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Cystatin C in pregnant women is not a simple kidney filtration marker

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Preeclampsia is pregnancy-specific systemic syndrome characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation. Approximately 5% of pregnancies are affected by preeclampsia worldwide. Although there have been many advances in the understanding of the pathophysiology of preeclampsia and the quality of obstetric care, preeclampsia is still a leading cause of maternal and fetal morbidity and mortality [1]. In addition, women undergoing preeclampsia are exposed to higher long-term cardiovascular and renal outcomes [2]. Aggressive screening, early diagnosis, and management are essential to reduce the instances of preeclampsia.

Although the definite pathophysiology of preeclampsia needs further study, insufficient placental function is considered to be leading cause of preeclampsia. The diseased placenta, in turn, secretes anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1, placental growth factors, and soluble endoglin and other toxic mediators into the systemic circulation, causing maternal endothelial dysfunction [3]. Those biomarkers have been suggested to play a role in predicting preeclampsia occurrences and adverse pregnancy outcomes, although their use is not widely applied in current clinical practice.

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The kidney, which is one of the most susceptible organs to endothelial dysfunction, is easily affected by altered placental function and its consequences. Kidney damage can be recognized simply by using kidney filtration markers or urine tests. Indeed, both proteinuria and renal insufficiency are included in the main diagnostic criteria for preeclampsia [4]. Also, a recent study demonstrated that gestational kidney function reported by estimated glomerular filtration rate (eGFR) can "predict" adverse pregnancy outcomes, including preeclampsia [5]. As such, simple kidney filtration markers can be easily used to recognize endothelial dysfunction in the early stage of preeclampsia before the affected women suffer from the typical symptoms or signs of preeclampsia.

In this issue of *Kidney Research and Clinical Practice*, Wattanavaekin et al [6] explored the role of cystatin C in a prospective cohort of 26 women with preeclampsia, all with a normal kidney function with serum creatinine 0.4 to 0.8 mg/dL. The authors found a marked difference between cystatin C-based and creatinine-based eGFR values. The cystatin C based eGFR value was less than half of the creatinine-based eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. About half of the preeclamptic women with normal renal function presenting with conventional serum creatinine-based eGFR had impaired renal function less than 60 mL/min/1.73 m^2 of cystatin-C based eGFR. Although this difference of eGFR values was not associated with adverse pregnancy outcomes represented by preterm birth, cystatin C itself was associated with preterm birth more closely in women with preeclampsia.

An accurate assessment of renal function in pregnant women has yet to be established. Inulin clearance is the gold standard for measuring renal function, although it is

cumbersome. Creatinine clearance is also useful, but the effects of physiologic hydronephrosis during pregnancy on urinary creatinine excretion should be considered. Most estimations of renal function represented by eGFR using filtration markers, including serum creatinine and cystatin C, were poorly validated in pregnant women. Serum creatinine is highly influenced by muscle mass, diet, and various drugs affecting tubular secretion of creatinine. Cystatin C, an endogenous inhibitor of cathepsin proteases, has been found to estimate renal function more sensitively than serum creatinine. Cystatin C is produced from nearly all nucleated cells at a constant rate. The level of cystatin C is not affected by muscle mass or diet but can be changed by thyroid hormones or high doses of the glucocorticoid hormone. However, cystatin C-based eGFR was not correlated with inulin clearance in pregnant women. This was thought to be due to placental production of cystatin C [7].

Of note, cystatin C may have a specific role in pregnant women. During the development of the placenta, cysteine protease production is essential to aid trophoblast invasion and angiogenesis into the decidua. Cystatin C, an inhibitor of the cysteine protease, allows decidua to limit trophoblast invasion. This protease-inhibitor balance is essential in the regulation of normal placenta development [8]. Several clinical studies have shown that cystatin C levels increased in mothers with preeclampsia when compared to those without it, even several months before its clinical manifestation [9]. Moreover, mRNA and protein expression of cystatin C were elevated in the preeclamptic placenta, which suggests that increased synthesis and secretion of cystatin C may contribute to the elevated maternal cystatin C levels in the women with preeclampsia [10].

In the present study, interestingly, Wattanavaekin et al [6] suggested an additional relevant role for cystatin C in women with preeclampsia independent of renal function. Even among women with preeclampsia, elevated cystatin C levels may predict adverse pregnancy outcomes, such as preterm birth. During pregnancy, cystatin C may not represent one of the simple kidney filtration markers, but it could be a novel biomarker for placental dysfunction. Further scientific evidence is required to support the role of kidney filtration markers predicting adverse pregnancy outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

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