Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease

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Women with chronic kidney disease (CKD) and chronic hypertension (CHT) frequently develop superimposed pre-eclampsia, but distinction from pre-existing disease is challenging. Plasma placental growth factor (PlGF), B-type natriuretic peptide (BNP), neutrophil gelatinase-associated lipocalin (NGAL), and serum relaxin concentrations were quantified in a longitudinal prospective cohort of 121 women with CKD: 44 with chronic hypertension, and 79 healthy controls. Biomarker concentrations were compared with 32 women with pre-eclampsia without pre-existing disease. Test performance was evaluated for diagnosis of superimposed pre-eclampsia requiring delivery within 14 days of sampling. PlGF was evaluated as a promising marker in a validation cohort of women with suspected pre-eclampsia (29 with CKD; 94 with chronic hypertension; 29 with superimposed pre-eclampsia requiring delivery within 14 days) and compared with women without pre-existing disease (290 with no pre-eclampsia and 176 with pre-eclampsia requiring delivery within 14 days). From 20 and up to 42 weeks of gestation, lower maternal PlGF concentrations had high diagnostic accuracy for superimposed pre-eclampsia requiring delivery within 14 days (receiver operator characteristic 0.85) and confirmed in the validation cohort. The other plasma and serum biomarkers were not discriminatory. Thus, plasma PlGF concentrations could potentially help guide clinical decision making regarding admission and delivery for superimposed pre-eclampsia.

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Pre-eclampsia is estimated to complicate 2% to 8% of all pregnancies[1]; however superimposed pre-eclampsia is reported to affect approximately 26% of pregnant women with chronic hypertension (CHT)[2] and 22% to 75% of women with chronic kidney disease (CKD).[3] The diagnosis of pre-eclampsia when superimposed on CKD and CHT is challenging because it may be clinically indistinguishable from benign gestational progression of pre-existing hypertension and proteinuria, which often coexist.[4] Superimposed pre-eclampsia is frequently associated with poor maternal and fetal outcomes. Therefore, early and accurate diagnosis is essential to allow timely intervention, whereas misdiagnosis may also lead to unnecessary admissions and iatrogenic preterm delivery.

Current hypotheses describe abnormal placental perfusion and predisposing maternal factors[5] (including cardiac, vascular, and renal dysfunction) in the genesis of pre-eclampsia, but the relevant contribution of placental and maternal influences to the development of superimposed pre-eclampsia is poorly understood. The aims of this study were to evaluate the predictive and diagnostic performance of markers of placental, cardiac, and renal function in superimposed pre-eclampsia, which have previously been implicated in pre-eclampsia in women without underlying disease.

The markers studied were placental growth factor (PlGF), soluble fms-like tyrosine kinase receptor (sFlt-1), B-type natriuretic peptide (BNP), neutrophil gelatinase–associated lipocalin (NGAL), and relaxin. PlGF, an angiogenic protein synthesized by syncytiotrophoblasts, increases in the blood of healthy pregnant women until 26 to 30 weeks of gestation and then falls toward term[6]; low plasma PlGF has been reported in women with pre-eclampsia.[7] Conversely sFlt-1, an anti-angiogenic protein that binds to PlGF and prevents interaction with endothelial receptors, is raised in women with pre-eclampsia.[8] Higher than normal concentrations of BNP[9,10] are observed in women with pre-eclampsia; BNP is released with cardiac ventricular strain and is raised before diagnosis in women with early-onset pre-eclampsia.[11] NGAL, an early marker of acute kidney injury, has been associated with pre-eclampsia in women without pre-existing disease,[12,13] and relaxin is an ovarian hormone known to play an important physiological role in renal adaptation to pregnancy.[14]

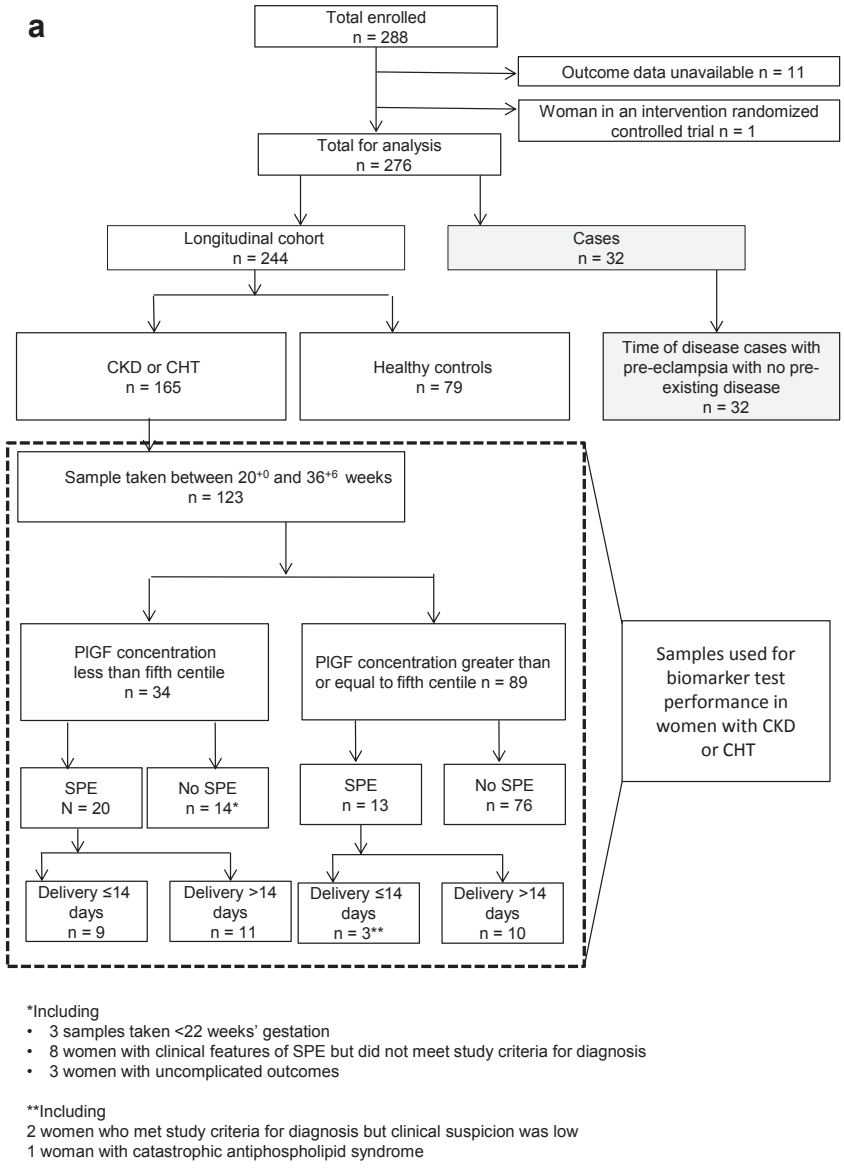

Figure 1 | (a) Longitudinal cohort: flow diagram of participants. (continued)

Measurement of these biomarkers was undertaken in 4 groups of women with CKD or CHT with superimposed pre-eclampsia, CKD or CHT without superimposed pre-eclampsia, pre-eclampsia without CKD or CHT and healthy controls. We validated the best performing marker in a second cohort of women with suspected pre-eclampsia or superimposed pre-eclampsia. The primary outcome of superimposed pre-eclampsia requiring delivery within 14 days was chosen to provide a clinically relevant end point that reflects current management strategies.[15]

RESULTS

Longitudinal cohort

Two hundred eighty-eight women were recruited to the study (Figure 1a). Of those who consented, 11 were lost to follow-up and 1 was subsequently recruited to a treatment trial for pre-eclampsia. The remaining 276 women provided 471 samples for analysis.

Demographics. Baseline demographic data are presented in Table 1. Details of underlying disease in women with CKD or CHT (or both) are shown in Supplementary Table S1 online. There were no demographic differences between women with CKD or CHT, or both, who did or did not experience superimposed pre-eclampsia.

Demographics for women with CKD or CHT (or both) according to severity of CKD are shown in Supplementary Table S2 online. Twenty-five (21.6%) of 121 women with CKD had the diagnosis of CKD made during the index pregnancy, including 6 of the 23 women (26%) with CKD who subsequently experienced superimposed pre-eclampsia.

Maternal outcomes. Maternal outcomes are shown in Table 2. Forty women (24.2%) were diagnosed with