Low urinary placental growth factor is a marker of pre-eclampsia

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Recent reports of increased serum levels of soluble fms-like tyrosine kinase 1 (sFlt-1) and decreased levels of placental growth factor (PlGF) suggest the key role of angiogenic factors in development of pre-eclampsia. PlGF is excreted in urine, and reduced urinary level has been suggested as a marker of this condition as well as help in its prediction. We measured urinary PlGF and creatinine values in 69 pregnant women (35 with pre-eclampsia and 34 normotensive controls). Over 70% patients had severe pre-eclampsia. Compared to controls, the urinary PlGF and PlGF/creatinine levels were significantly reduced in women with pre-eclampsia. The hospital stay was longer and fetal outcomes poorer in this group. Three normotensive women who showed very low levels developed pre-eclampsia 2–6 weeks later. Reduced urinary PlGF level in a pregnant woman is a marker of pre-eclampsia. The value of reduced urinary PlGF levels in predicting pre-eclampsia in currently normotensive pregnant women needs to be evaluated. A simple predictive test is likely to be of value in the developing countries.

Kidney International (2006) **69,** 621–624. doi:10.1038/sj.ki.5000075; published online 4 January 2006

KEYWORDS: pre-eclampsia; placental growth factor; urinary biomarker; diagnosis

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Received 17 May 2005; revised 27 July 2005; accepted 11 August 2005; published online 4 January 2006

Pre-eclampsia, a pregnancy-specific syndrome characterized by hypertension, proteinuria, and edema, is the leading cause of maternal and perinatal morbidity and mortality.[1,2] Pre-eclampsia occurs only in the presence of placenta and its resolution begins with the removal of placenta.

Recent investigations indicate that imbalance of angiogenic factors may be responsible for at least two of pre-eclampsia's penotypes, hypertension, and proteinuria.[3–10] Levels of circulatory soluble fms-like tyrosine kinase 1 (sFlt-1, also referred to as sVEGFR1) are increased, which may then bind the proangiogenic vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), thereby preventing their interaction with endothelial cell-surface receptors.[11] Infusion of adenoviruses transfected with sFlt-1 messenger ribonucleic acid in rats was followed by increased circulating sFlt-1 levels and appearance of hypertension, glomerular endotheliosis and proteinuria, the hallmarks of pre-eclampsia.[5,12] Elevated sFlt-1 and decreased free PlGF and VEGF antedated the clinical signs.[3,5,13] However, routine measurement of these angiogenic mediators for ascertaining the risk of pre-eclampsia could be difficult, and an alternative, less invasive method more suited to routine clinical use is required.

In contrast to the large (110 kDa) sFlt-1, PlGF (30 kDa) and VEGF (45 kDa) cross the glomerular filtration barrier and appear in urine. Podocytes and tubular cells produce VEGF,[14,15] and hence urinary VEGF cannot reflect circulating VEGF levels. In contrast, urinary PlGF is derived entirely from circulating blood and hence is likely to reflect the circulating angiogenic state. We examined the utility of reduced urinary PlGF as a marker of pre-eclampsia.

RESULTS

Table 1 shows the clinical characteristics of controls and those with pre-eclampsia. There were no significant differences between groups in the maternal age and gestational age at the time of sampling. In all, 25 (71%) patients had severe pre-eclampsia at presentation. The pre-eclampsia group showed significantly lower urinary PlGF levels (18 ± 11.3 vs 205.8 ± 132.2 pg/ml, $P < 0.0001$) and PlGF/creatinine ratio (26.1 ± 16 *vs* 258.5 ± 130.5 pg/mg, $P < 0.0001$). Figure 1 shows the PlGF and PlGF/creatinine ratios according to the

Table 1 | Clinical parameters of normotensive pregnant women (controls) and those with preeclampsia

	<32 weeks		>32 weeks	
	Control (*n*=14)	Pre-eclampsia (*n*=15)	Control (*n*=17)	Pre-eclampsia (*n*=20)
Period of gestation				
Maternal age (years)	26.9±5.06	26.13±4.22	26.53±4.31	25.75±4.18
Gestational age (weeks)	30.16±0.89	30.28±1.28	34.3±1.53	34.56±1.18
Severe pre-eclampsia	—	12 (80%)	—	13 (65%)
Blood pressure (mmHg)				
Systolic	114.7±5.54	170.2±19.06*	110.68±7.96	162.3±12.62*
Diastolic	76.93±3.78	107.6±10.31*	78.47±4.36	105.4±9.94*
Uric Acid (mg/dl)	3.48±0.91	5.97±1.38*	4.22±1.02	6.64±1.6*

*$P<0.001$ compared to control.

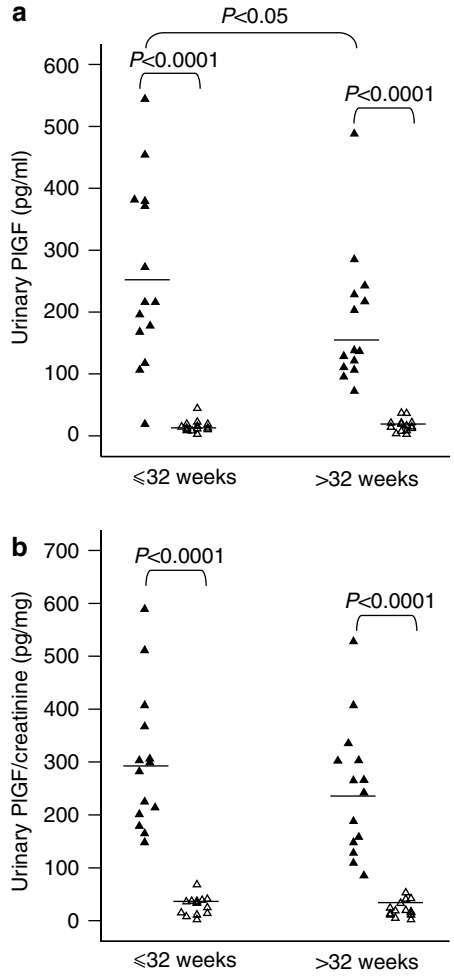

Figure 1 | Scattergram of (a) urinary PlGF and (b) urinary PlGF after normalization for urinary creatinine in pregnant women ≤32 weeks and after 32 weeks of gestation. Solid triangles represent the normotensive control group and open triangles those with pre-eclampsia. Horizontal lines in each group represent the mean values.

gestational age. The mean PlGF levels were 15 and 10 times lower before and after 32 weeks of gestation in the pre-eclampsia group. PlGF normalized for urinary creatinine was 10- and 11-fold lower in ≤32- and >32-week gestational age groups, respectively. PlGF values were lower in normotensive pregnancies after 32 weeks of gestation ($P=0.048$). In the three normotensive women who developed pre-eclampsia later, the urine PlGF (18.3, 16.4 and 21.2 pg/ml) and PlGF/creatinine (14.6, 25.5 and 17.1 pg/mg) levels were similar to those noted in those with pre-eclampsia. *Post-hoc* power analysis showed that the study had >90% power to detect difference between the different subgroups at 1% significance level.

Among the pre-eclamptic women, reduced urinary PlGF showed a significant correlation with elevated serum uric acid ($P=0.031$) and IUGR ($P=0.046$), but there was no correlation with systolic and diastolic blood pressures or severity of proteinuria.

Of the 31 normotensive women, three delivered before 37 weeks of gestation. Two had small-for-gestational-age babies. Out of the 35 cases with pre-eclampsia, 23 required delivery within 24 h of presentation. Live infants of appropriate weight for gestational age were delivered in 19 cases, 10 had small-for-gestational-age infants and six ended in stillbirths. Four infants required transfer to the neonatal intensive care unit. Women with pre-eclampsia had a significantly longer hospital stay (3.2±1.1 *vs* 0.9±0.3 days, $P<0.01$).

DISCUSSION

This prospective study confirms the hypothesis that urinary concentrations of PlGF are significantly lower in pregnant women with pre-eclampsia compared to normotensive controls. The difference is maintained after normalization for urinary creatinine concentrations. PlGF levels are lower in normotensive pregnant women after 32 weeks of gestation; hence, values in disease states should be compared with normal values at the appropriate gestation age. We found that urinary PlGF could differentiate women with pre-eclampsia from normotensive controls in our population (women from India), and confirmed the findings of Levine *et al.*[10] Reduced urinary PlGF level antedated the diagnosis of pre-eclampsia by several weeks in their cohort, a phenomenon noted in three cases in the present study too. These findings suggest that this test may be useful for predicting this disorder. This hypothesis needs to be tested prospectively in larger number of cases. A limitation of this study was the lack of patient