Effective prediction of preeclampsia by measuring serum angiotensin II, urinary angiotensinogen and urinary transforming growth factor β1

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Received September 5, 2015; Accepted January 26, 2017

DOI: 10.3892/etm.2017.4484

Abstract. The aim of the current study was to analyze serum angiotensin II (Ang II), urinary angiotensinogen (AGT) and urinary transforming growth factor β1 (TGFβ1) levels in relation to the clinical manifestation of preeclampsia, and to explore the effects of circulating and renal renin angiotensin system (RAS) in preeclampsia patients. An enzyme-linked immunosorbent assay was used to evaluate serum Ang II, urinary AGT and urinary TGFβ1 in preeclampsia, pregnancy-induced hypertension and normotensive pregnancy patients. The correlation between urinary AGT and serum Ang II, urinary TGFβ1, blood pressure and urinary albumin/creatinine ratio (ACR) were then analyzed. Receiver operating characteristic (ROC) curves were also constructed. Negative correlations were observed between urinary AGT and blood pressure, and urinary AGT and ACR, whereas positive correlations were found between urinary AGT and serum Ang II, and urinary AFT and TGFβ1. Moreover, the area under the curve (AUC) of AGT was 0.841 [95% confidence interval (CI): 0.742-0.940, P<0.001], which was significantly higher than that of serum Ang II or urinary TGFβ1 (P<0.001). The optimal cut-off value of urinary AGT at 193 ng/l showed a high diagnostic value in preeclampsia. The AUC of combined serum Ang II, urinary AGT and urinary TGFβ1 was 0.918 (95% CI: 0.845-0.990, P<0.001), with a sensitivity of 83.9% and a specificity of 89.7%. Decreased levels of urinary AGT in preeclampsia patients suggested that local renal RAS was suppressed, and this was associated with hypertension and proteinuria. A high value preeclampsia diagnosis could be achieved by measuring urinary AGT or a combination of urinary AGT, serum Ang II and urinary TGFβ1.

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Key words: angiotensin II, angiotensinogen, transforming growth factor β1, preeclampsia, receiver operating characteristic curve

Introduction

Preeclampsia, a pregnancy-specific disorder affecting ~5% of all pregnancies, is a leading cause of maternal and neonatal morbidity and mortality during pregnancy (1,2). It is characterized by hypertension and proteinuria after 20 weeks of gestation (3). The exact pathogenesis of preeclampsia remains unclear, and it is reported that the renin-angiotensin system (RAS), a major blood pressure regulating system, plays a critical role in the development of preeclampsia (4).

As a key signaling cascade, the circulating RAS is classically described in the kidney. Renin is an enzyme synthesized and released by juxtaglomerular cells of the afferent renal arterioles. It is involved in blood pressure and sodium chloride regulation (4). In RAS, renin can cleave angiotensinogen (AGT) to produce angiotensin I (Ang I) and is a rate-limiting factor in the RAS cascade (4). Ang I is then cleaved by angiotensin-converting enzyme (ACE) to produce the effector molecule angiotensin II (Ang II), which could eventually affect the function of vascular smooth muscle cells and adrenal glands (5). According to previous reports (6,7), decreased levels of renin, Ang I and Ang II and increased levels of ACE and Ang II sensitivity are observed in preeclampsia.

In addition to RAS, endothelial dysfunction caused by abnormal placentation is reported to be closely related to the development of preeclampsia (8). Transforming growth factor beta (TGF-β) is a major cytokine produced abundantly in vascular endothelial cells and trophoblasts. It plays a key role in various physiological processes, including embryonic growth and development, inflammation repair and angiogenesis (9-12). TGF-β1, one of three isoforms of TGF-β, is a key mediator in vascular endothelial cell apoptosis and proliferation, immunosuppression and cellular matrix synthesis (13-15). Moreover, TGF-β1 participates in successful placentation through trophoblast invasion regulation (16-18) and its levels are higher in pregnant women than in non-pregnant women (19). Ayatollahi *et al* demonstrated that TGF-β1 is a regulatory factor in fetal allograft survival during pregnancy (19).

As the source and target cells of urinary TGF-β1, renal cells could be regulated by TGF-β1. Murakami *et al* (20) demonstrated that significantly higher levels of urinary TGF-β are found in patients with IgA nephritis and focal

glomerulosclerosis, compared with patients with other types of glomerular diseases and healthy controls. In patients with proliferative-type diseases, urinary TGF-β was significantly correlated with the grade of mesangial matrix increase and the magnitude of proteinuria. Their results indicated that urinary TGF-β could reflect the grade of interstitial fibrosis in glomerular diseases and the mesangial matrix increased in proliferative-type glomerulonephritis (20). Measuring TGF-β levels in the urine might be helpful in monitoring patients with renal disease. Previous results have also suggested that renal TGFβ1 is associated with proteinuria in pregnancy-induced hypertension (21).

The current study aimed to analyze serum Ang II, urinary AGT and urinary TGFβ1 levels in relation to the clinical manifestation of preeclampsia, and to explore the effects of circulating RAS on preeclampsia and proteinuria development.

Materials and methods

Patients and controls. A total of 83 pregnant women were recruited between December 2007 and March 2010 and assigned to one of three groups: Group A (n=33), preeclampsia; Group B (n=19), pregnancy-induced hypertension; or Group C (n=31), normotensive pregnancy. All of the participants were of Chinese origin and were pregnant with a single fetus. The protocol was approved by the Ethics Committee of The Fifth People's Hospital of Shanghai, Fudan University (Shanghai, China). Written informed consent was obtained from all participants.

Preeclampsia was defined as follows: i) Sustained systolic blood pressure of >140 mmHg or a sustained diastolic blood pressure of >90 mmHg on two separate readings; ii) proteinuria measurement of ≥1+ or 24-h urine protein collection of >300 mg. Pregnancy-induced hypertension was defined as hypertension (>140/90 mmHg) during the pregnancy period that was resolved 12 weeks later, with no proteinuria. Normal pregnancy was defined as normal blood pressure (<140/90 mmHg) during the pregnancy period with no proteinuria or obstetric and medical complications.

Blood and urinary sampling. Blood samples were collected into tubes containing EDTA as an anticoagulant. Plasma samples were obtained by centrifugation at 3,000 x g for 10 min. Aliquots of samples were prepared, stored at -80˚C and used within 12 weeks. Morning spot urine samples were collected from all subjects for laboratory analysis. Collected 24-h urine was used for quantitation of daily urinary protein excretion.

Laboratory analysis. Serum alanine aminotransaminase, albumin (Alb), creatinine (Scr), urea nitrogen (BUN) uric acid (UA) and albumin/creatinine ratio (ACR), as well as estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease formula) and 24-h urine protein quantification were determined using an Automatic Biochemistry Analyzer (Roche Modular P800; Roche Diagnostics GmbH, Mannheim, Germany).

Serum Ang II, urinary AGT and urinary TGFβ1 determination. Levels of Ang II, AGT and TGFβ1 were determined using a commercially available enzyme-linked immunosorbent assay (ELISA; R&D Systems, Inc., Minneapolis, MN, USA), according to the manufacturer's instructions. All samples were run in duplicate on the assay plate. If >10% variation existed between duplicates, the assay was repeated and the average was reported.

Statistical analysis. All statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Measurement and enumeration data are expressed as the mean ± standard deviation. Mann-Whitney U and χ^2 tests were employed to compare variables between two groups. Multiple group comparisons were performed by analysis of variance and further comparisons between two groups were performed with post-hoc tests. Correlations were calculated using Spearman's rank correlation. Receiver operating characteristic (ROC) curve analysis was used to assess the optimal cut-off value of one or two combined factors for preeclampsia prediction. Overall accuracy was estimated using area under the curve (AUC). MedCalc statistical software version 13.0 (MedCalc Software bvba, Ostend, Belgium) was used to compare the AUCs of different ROC curves. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient demographic data. The patient demographic data are shown in Table I. Significantly decreased Alb and eGFR were found in preeclampsia patients compared with group B (both $P<0.05$) and significantly increased Scr, BUN, UA and ACR (all $P<0.05$) were found in preeclampsia patients compared with group C.

Comparison of serum Ang II, urinary AGT and urinary TGFβ1. Serum Ang II, urinary AGT and urinary TGFβ1 levels were evaluated using ELISA. The results showed a significantly decreased level of AGT in preeclampsia patients as compared with pregnancy-induced hypertension ($P<0.05$) and normotensive pregnancy patients ($P<0.05$; Table II). Moreover, an increased TGF-β1 level was observed in preeclampsia patients, although this result was not significant when compared with pregnancy-induced hypertension or normotensive pregnancy patients.

Correlation analysis. Correlation analysis was performed for all participants between urinary AGT and ACR, systolic and diastolic blood pressure (SBP and DBP, respectively), serum Ang II and urinary TGFβ1 (Fig. 1). A negative correlation was found between AGT and ACR ($r=-0.302$, $P=0.004$); AGT and blood pressure ($r_{SBP}=-0.275$, $P=0.009$; $r_{DBP}=-0.279$, $P=0.008$); a positive correlation was found between AGT and Ang II ($r=0.255$, $P=0.015$); a positive correlation was found between AGT and TGFβ1 ($r=0.386$, $P<0.001$).

Utility of serum Ang II and/or urinary TGFβ1 and AGT in predicting preeclampsia. The performance of serum Ang II, urinary TGFβ1 and AGT in preeclampsia prediction were used to construct ROC curves (Fig. 2). The results showed that the AUC of urinary AGT was 0.841 (95% CI: 0.742-0.940, $P<0.001$), which was significantly higher than that of urinary

Table I. Demographic data of included subjects.

Characteristics	Group A (n=33)	Group B (n=19)	Group C (n=31)
Age (years)	28 (24-32)	28 (23.5-35)	27 (25-29)
SBP (mmHg)	150 (145-160)	140 (140-150)	120 (110-120)
DBP (mmHg)	100 (95-110)	100 (90-100)	75 (70-80)
ALT (U/l)	9 (8-14)	10 (7-13)	11 (10-15)
Alb (g/l)	30.4 (26.5-34.5)[a]	36.4 (31.8-39.1)	38.0 (35.8-39.1)
Scr (μmol/l)	48 (43-55)[b]	47 (43-52)	45 (40-48)
BUN (mmol/l)	3.8 (3.0-5.1)[b]	3.5 (3.0-3.9)	2.9 (2.6-3.3)
UA (μmol/l)	315 (254-420)[b]	260 (247-297)	265 (221-296)
eGFR (ml/min)	134.08 (105.66-160.19)[a]	148.55 (140.05-161.53)	167.41 (154.55-184.88)
ACR (mg/mmol)	31.05 (12.00-121.10)[b]	3.70 (1.11-5.94)	1.98 (0.89-4.44)

All data are presented as the median (interquartile range). Group A, preeclampsia; Group B, pregnancy-induced hypertension; Group C, normotensive pregnancy. SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransaminase; Alb, albumin; Scr, creatinine; BUN, blood urea nitrogen; UA, uric acid; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio. [a]P<0.05 vs. Group B and [b]P<0.05 vs. Group C.

Table II. Serum Ang II, urinary TGFβ1 and urinary AGT levels among different groups of subjects.

Characteristics	Group A (n=33)	Group B (n=19)	Group C (n=31)
Serum Ang II (ng/l)	70.81±16.68	70.29±11.97	68.08±11.85
Urinary TGFβ1 (ng/l)	433.25±139.77	403.09±63.87	401.79±106.39
Urinary AGT (ng/l)	185.72±30.43[a,b]	201.65±17.60	205.11±22.25

Group A, preeclampsia patients; Group B, pregnancy-induced hypertension patients; Group C, normotensive pregnancy patients. [a]P<0.05 vs. Group C, [b]P<0.05 vs. Group B. Ang II, angiotensin II; AGT, angiotensinogen; TGFβ1, transforming growth factor β1.

TGFβ1 (AUC=0.613, 95% CI: 0.467-0.759, P=0.133) and serum Ang II (AUC=0.647, 95% CI: 0.507-0.787, P=0.05). Moreover, the optimal cut-off value of urinary AGT was determined. The results showed that urinary AGT=193 ng/l exhibited the highest sensitivity and specificity in preeclampsia diagnosis (Tables III-V).

In order to improve the sensitivity and specificity of preeclampsia prediction, ROC curves were also constructed for combinations of urinary AGT, urinary TGFβ1 and serum Ang II (Fig. 3, Table VI). The results showed that the AUC for urinary AGT + urinary TGFβ1 was 0.806 (95% CI: 0.777-0.959, P<0.001); the AUC for urinary AGT + serum Ang II was 0.901 (95% CI: 0.822-0.980, P<0.001); the AUC for serum Ang II+urinary TGFβ1 was 0.684 (95% CI: 0.549-0.819, P=0.014); and the AUC for urinary AGT + serum Ang II + urinary TGFβ1 was 0.918 (95% CI: 0.845-0.990, P<0.001).

Discussion

To the best of our knowledge, this was the first study to explore the expression of RAS in the kidney in patients with preeclampsia and the value of urinary AGT in preeclampsia diagnosis. A decreased level of urinary AGT was found in preeclampsia patients and this was associated with hypertension and proteinuria. It was proposed that a high value of preeclampsia diagnosis could be achieved using urinary AGT or a combination of urinary AGT, serum Ang II and urinary TGFβ1.

Senatorski *et al* (22) showed that higher levels of urinary TGF-β1 could be found in membranous glomerulonephritis patients compared with a control group. In the current study, elevated urinary TGFβ1 was observed in preeclampsia patients compared with normotensive pregnancy patients, but this result was not considered to be significant. Moreover, no linear correlation was found between urinary TGFβ1 and ACR. In addition, an ROC curve indicated that urinary TGFβ1 had a lower diagnostic value in preeclampsia compared with urinary AGT. This discrepancy with previous results could be attributed to a smaller sample size. Furthermore, Blush *et al* (23) demonstrated that estradiol administration to Alb/TGF-β transgenic mice (which overexpress TGF-β) could ameliorate progressive renal injury. Estradiol was able to reverse the pro-fibrotic effects of TGF-β, which could help to explain the sexual dimorphism in renal disease progression observed in humans (23). Furthermore, Potier *et al* (24) showed that 17beta-estradiol increased both matrix metalloproteinase 9 (MMP9) mRNA and MMP-9 activity in mesangial cells. Therefore, the protective effect exerted by the hormone during pregnancy may be the reason for

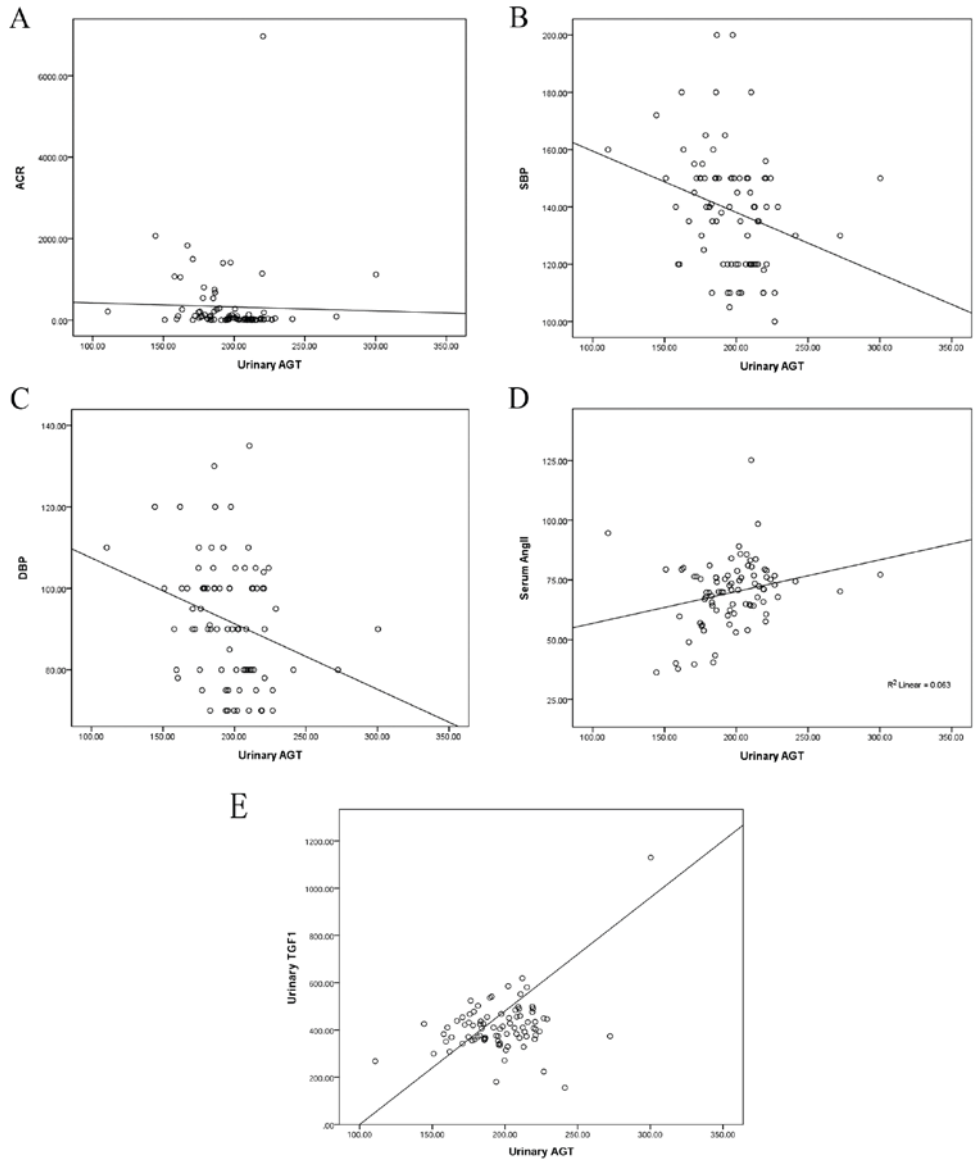

Figure 1. Correlation analysis between urinary AGT and ACR, SBP, DBP, serum Ang II and urinary TGFβ1. (A) Correlation between AGT and ACR (r=-0.302, P=0.004). (B) Correlation between AGT and SBP (r=-0.275, P=0.009). (C) Correlation between AGT and DBP (r=-0.279, P=0.008). (D) Correlation between AGT and serum Ang II (r=0.255, P=0.015). (E) Correlation between AGT and TGFβ1 (r=0.386, P=0.000). AGT, angiotensinogen; ACR, albumin/creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; Ang II, angiotensin II; TGFβ, transforming growth factor β1.

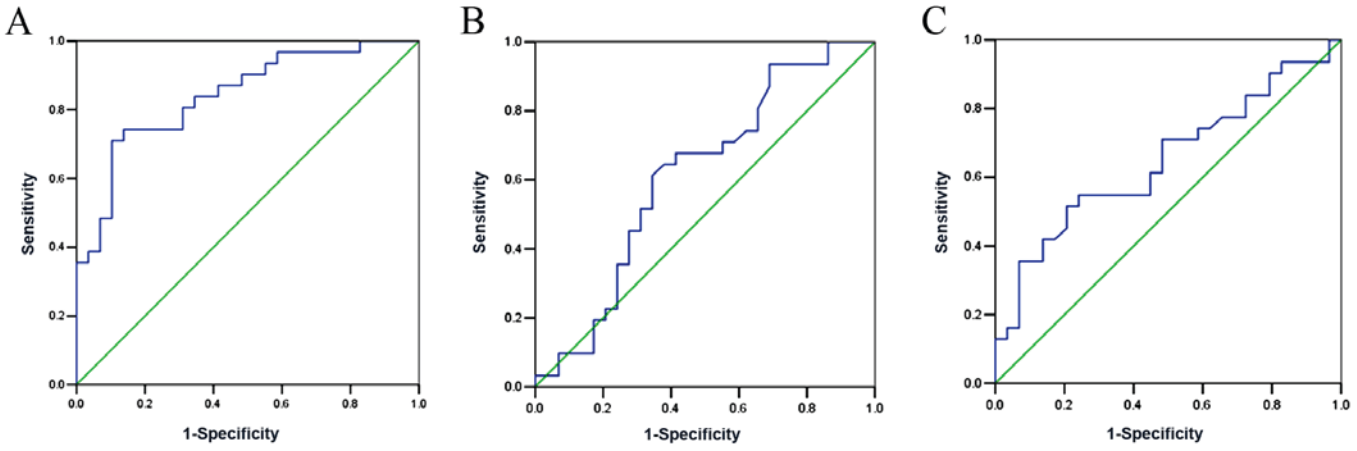

Figure 2. Receiver operating characteristic curves for urinary AGT, urinary TGFβ1 and serum Ang II as diagnostic indicators of preeclampsia. (A) Urinary AGT. AUC=0.841 (95% CI: 0.742-0.940, P<0.001). (B) Urinary TGFβ1. AUC=0.613 (95% CI: 0.467-0.759, P=0.133). (C) Urinary Ang II. AUC=0.647 (95% CI: 0.507-0.787, P=0.05). AGT, angiotensinogen; Ang II, angiotensin II; TGFβ, transforming growth factor β1; AUC, area under the curve; CI, confidence interval.

Table III. Performance of different cut-off values of urinary angiotensinogen for diagnosis of preeclampsia.

Cut-off value (ng/l)	Sensitivity (%)	Specificity (%)
175	35.5	100
180	45.2	93.1
193	74.2	86.2
200	80.6	65.5
210	93.5	44.8
220	100	17.2

Table IV. Performance of different cut-off values of urinary transforming growth factor β1 for diagnosis of preeclampsia.

Cut-off value (ng/l)	Sensitivity (%)	Specificity (%)
289	100	13.8
356	93.5	31.0
380	71.0	44.8
425	51.6	69.0
468	22.6	79.3
841	3.2	100

Table V. Performance of different cut-off values of serum angiotensin II for diagnosis of preeclampsia.

Cut-off value (ng/l)	Sensitivity (%)	Specificity (%)
40	100	3.4
60	83.9	27.6
65	71.0	51.7
75	54.8	75.9
80	19.4	93.1
85	12.9	100

Table VI. Performance of combination tests for diagnosis of preeclampsia.

Combination of biomarkers	Sensitivity (%)	Specificity (%)
Urinary AGT + urinary TGFβ1	80.6	86.2
Urinary AGT + serum Ang II	71.0	62.1
Serum Ang II + urinary TGFβ1	80.6	79.3
Urinary AGT + serum Ang II + urinary TGFβ1	83.9	89.7

AGT, angiotensinogen; TGFβ1, transforming growth factor β1; Ang II, angiotensin II.

decreased renal fibrosis. However, further study should be conducted to elucidate the role of TGFβ1 in patients with pregnancy-induced hypertension.

All the components of RAS are known to be present in the uterine placenta, as previous studies have confirmed the expression of the renin gene in the human placenta, villus and uterus (25,26), and observed higher levels of GFR, plasma renin (PRC) and plasma aldosterone during normal pregnancy compared with non-pregnancy (27). Inhibition of ACE was able to effectively control the conversion of Ang I to Ang II, reduce the inactivation of bradykinin (BK) and stimulate the production of prostaglandin I2 and estradiol. Therefore, decreasing the sensitivity of vessel walls to Ang II could assist in maintaining a balance of blood pressure (28). Previously, decreased PRC and increased ACR activity was observed in normal pregnancy (29). Increased activity of serum ACE could result in BK inactivation and inhibition of NO release, thereby leading to endothelial damage.

Alexander *et al* (30) observed no significant difference in the efficacy of oral captopril treatment for lowering mean arterial blood pressure between normal pregnancy and long-term uterus hypoperfusion pregnancy in rats, indicating that RAS did not play a major role in mediating the hypertension produced by chronic uterine perfusion pressure in pregnancy. However, RAS was highly likely to be involved in the pathophysiological process of preeclampsia, as activation of local RAS in the uterine placenta could result in preeclampsia (30). In the current study, a higher level of serum Ang II was observed in preeclampsia pregnancy patients than in pregnancy-induced hypertension or normal pregnancy patients, but this result was not considered to be significant. However, no correlation was found between serum Ang II and 24-h urinary protein quantification or ACR. In addition, the ROC curve indicated a lower diagnostic value of urinary serum Ang II in compared with urinary AGT. This discrepancy with previous results could be attributed to a smaller sample size.

Kobori *et al* (31) reported that Ang II-dependent hypertension could result in elevated intrarenal Ang II and AGT levels, reflected by increased urinary AGT, but that this did not occur in an Ang II-independent hypertensive model. In the current study, a significantly decreased level of urinary AGT was observed in preeclampsia patients compared with normal pregnancy or pregnancy-induced hypertension patients. A negative correlation was also found between urinary AGT and blood pressure in pregnant women, which indicated that inhibition of local renal RAS was associated with the development of hypertension and proteinuria in patients with preeclampsia. It is proposed that preeclampsia might be similar to the two kidney-one clip model in hypertensive animal models (32). In normal pregnancy, reduced blood flow to the placenta may result in the activation of RAS, while in preeclampsia, blood flow may not be reduced and therefore RAS activity may be inhibited. The ROC curve also indicated a high sensitivity and specificity of urinary AGT in the diagnosis of preeclampsia. The combined use of urinary AGT, serum Ang II and urinary TGFβ1 further improves the diagnostic value for preeclampsia. Due to the relative ease of collecting urine from patients, urinary AGT might be readily used as an indicator for preeclampsia diagnosis in clinical practice.

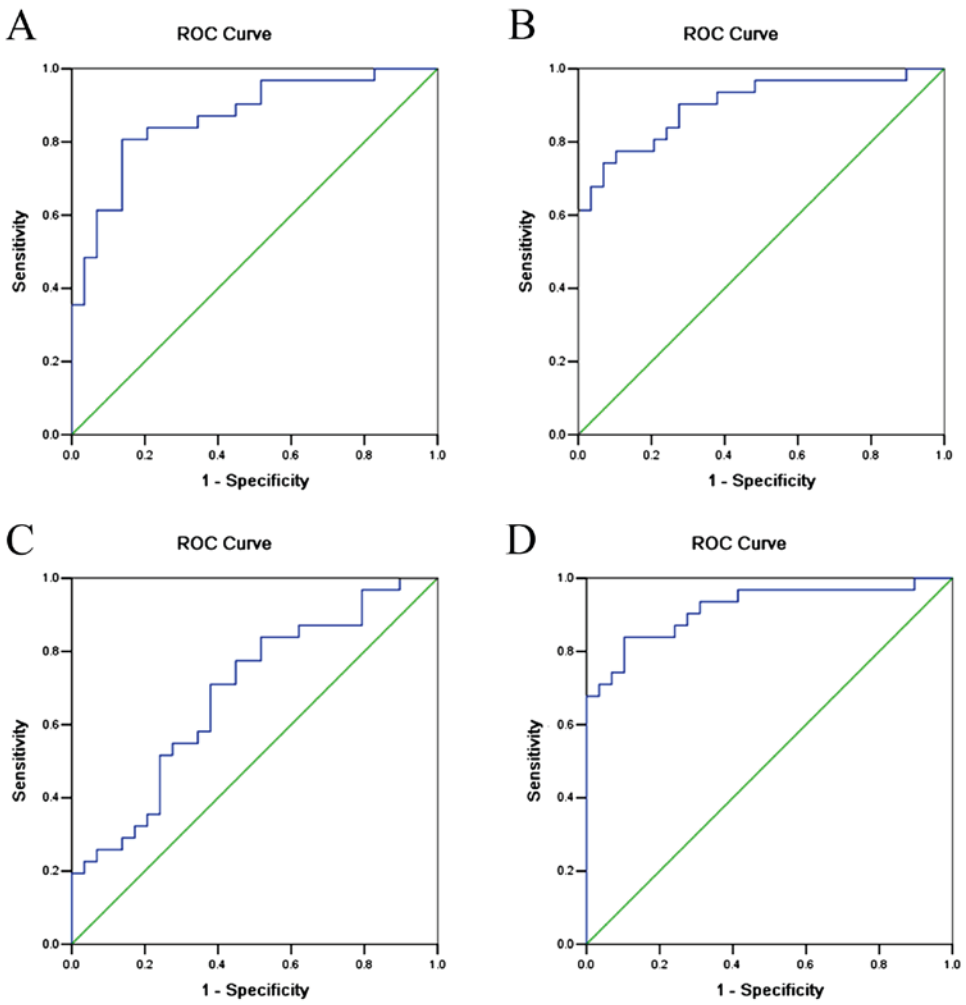

Figure 3. ROC curves for combining urinary AGT, TGFβ1 and serum Ang II as diagnostic indicators of preeclampsia. (A) Combined urinary AGT and urinary TGFβ1. AUC=0.806 (95% CI: 0.777-0.959, P<0.001). (B) Combined urinary AGT and serum Ang II. AUC=0.901 (95% CI: 0.822-0.980, P<0.001). (C) Combined urinary TGFβ1 and serum Ang II. AUC=0.684 (95% CI: 0.549-0.819, P=0.014). (D) Combined urinary AGT, serum Ang II and urinary TGFβ1. AUC=0.918 (95% CI: 0.845-0.990, P<0.001). AGT, angiotensinogen; Ang II, angiotensin II; TGFβ, transforming growth factor β1; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

The current study had a number of limitations. First, it is a single center study with a relatively small sample size. Further studies with larger samples in multiple centers should be performed in order to confirm the current results. Second, a cross-sectional design in the second trimester could have resulted in patient selection bias.

In conclusion, the current results help to elucidate the mechanisms of preeclampsia, kidney injury and proteinuria. Subsequent studies are needed to investigate the relationship between local placental RAS and circulating and local renal RAS in preeclampsia and the expression of local renal RAS components. A systemic analysis of RAS components in animal model and human subjects is also required.

Acknowledgements

This study was funded by the Shanghai Municipal Science and Technology Project (grant no. 124119a7802), the Fudan University Project 985 key discipline construction project (grant no. 2012FDYSXK02), the Shanghai City Health Bureau Project (grant no. 20114311), the Major State Basic Research Development Program of China (973 Program; grant no. 2012CB517700), Minhang District Natural Fund (grant no. 2013MHZ015), Phase III of the Nephropathy Discipline Construction of 211 Project of State Education Commission and the Minhang District key discipline construction project and the Hospital Youth Fund (grant no. 2010QJ02).

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