BASIC SCIENCE: OBSTETRICS

Plasma level of soluble c-Met is tightly associated with the clinical risk of preeclampsia

Xin Zeng, PhD; Yu Sun, MD; Hui-xia Yang, MD; Dong Li, BS; Yu-xia Li, BS; Qin-ping Liao, MD; Yan-ling Wang, PhD

OBJECTIVE: The objective of the study was to examine the relevance of the soluble form c-Met (sMet) with the clinical risk for severe preeclampsia.

STUDY DESIGN: This prospective case-control study was performed by using plasma derived from 44 preeclamptic and 51 uncomplicated pregnant women. Plasma concentration of sMet was measured with specific enzyme-linked immunosorbent assay, and the predictive values were determined based on the receiver-operating characteristic (ROC) curves analysis.

RESULTS: Plasma s-Met level in normal pregnant women changed in a gestation-dependent manner, peaking at weeks 19-24. In women with severe preeclampsia, the circulating sMet level was significantly lower than that in the gestational stage-matched controls during gestational weeks 15-30. The ROC curve analysis revealed a significant correlation between plasma sMet level and the risk of developing severe preeclampsia.

CONCLUSION: Plasma sMet could serve as a potential biomarker for predicting severe preeclampia at early second trimester of pregnancy.

Key words: predictive values, preeclampsia, receiver-operating characteristic curve analysis, soluble c-Met

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Preeclampsia is a pregnancy-specific syndrome that is characterized by maternal hypertension and proteinuria occurring after the 20th week of gestation. It is observed in 2-6% of all pregnancies worldwide and is responsible for a large proportion of fetal and maternal morbidity and mortality.[1,2] Until recently the etiology and pathogenesis of preeclampsia was not well understood, and the appropriate markers for early diagnosis of preeclampsia were poorly explored. However, it is widely accepted that preeclampsia is initiated by shallow placentation and incomplete to failed spiral artery remodeling, resulting in an imbalance of circulating angiogenic factors that further leads to maternal endothelial dysfunction.[3-7]

Several studies have provided evidences that preeclampsia is associated with elevated circulating concentrations of soluble fms-like tyrosine kinase receptor-1 (sFlt-1) and soluble endoglin (sEng), which are the truncated forms of the receptors for vascular endothelial growth factor (VEGF)[8,9] and transforming growth factor (TGF)-β,[10] respectively. They can prevent the interaction of VEGF (as well as placental growth factor [PlGF]) and TGF-β with their corresponding receptors on the cell surface by adhering to their receptor-binding domains.

Soluble Flt1 and sEng are mainly secreted by the placenta during pregnancy and are proved to increase in the maternal circulation weeks before the onset of preeclampsia. Evidences in animal studies demonstrate that these antiangiogenic factors produce systemic endothelial dysfunction, resulting in hypertension, proteinuria, and the other manifestations of preeclampsia.[6,10]

Hepatocyte growth factor (HGF), also called scatter factor, is a cytokine that regulates cell growth, differentiation, and morphogenesis in various tissues. It is also a potent angiogenic factor that stimulates the proliferation and migration of endothelial[11] and smooth muscle cells[12] and promotes the formation of new blood vessels in murine subcutaneous tissue and rat cornea angiogenesis models.[13]

The receptor for HGF, c-Met, is a heterodimer composed of a 50 kDa α-chain and a 140 kDa β-chain linked via disulfide bonds. The α-subunit is entirely extracellular and highly glycosylated, and the β-subunit is comprised of a large ex-

From the State Key Laboratory of Reproductive Biology, Institute of Zoology (Dr Zeng, Mr D. Li, Ms Y-x Li, and Dr Wang), and the Graduate School (Dr Zeng and Mr D. Li), Chinese Academy of Sciences, and the Department of Obstetrics and Gynecology (Drs Sun, Yang, and Liao), Peking University First Hospital, Beijing, China.

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Reprints: Yan-ling Wang, PhD, State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, 1 Beichen West Rd., Beijing 100101, China, or Qin-ping Liao, MD, Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing100034, China. wangyl@ioz.ac.cn or qinping_liao@hotmail.com.

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The first 2 authors contributed equally to this article.

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TABLE 1
Clinical characteristics of the women enrolled in this study

Characteristic	Normal pregnancy (n = 51)	Preeclampsia (n = 44)	*P* value
Maternal age, y	29.8 ± 3.2	30.8 ± 5.1	.28
BMI, kg/m^2	21.9 ± 2.6	22.6 ± 2.7	.25
Systolic blood pressure, mm Hg	105.3 ± 9.9	151.6 ± 12.8[a]	< .0001
Diastolic blood pressure, mm Hg	67.9 ± 6.9	100.1 ± 6.8[a]	< .0001
50 g GCT, mmol/L	6.8 ± 1.4	6.8 ± 2.0	.86
24 hour urine protein, g	NA	2.97 ± 3.02	NA
Primiparous percentage, %	98.4	95.5	NA
Gestational day at delivery, d	275 ± 9	260 ± 18[a]	.007
Infant birthweight, g	3354 ± 342	3042 ± 812	.1154

Data are shown in mean ± SD, and significant difference between groups was analyzed with Student *t* test.
BMI, body mass index, indicating the weight in kilograms divided by the square of the height in meters. *GCT*, glucose challenge test; *NA*, not available.

[a] Compared with normal pregnancy ($P < .05$).

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tracellular region, a transmembrane segment, and an intracellular tyrosine kinase domain.[14] Evidences have revealed that the integral c-Met can be released from the endothelial cell membrane by proteolysis to form a soluble, truncated protein (sMet), which is able to bind HGF and disrupt HGF/c-Met signaling.[15]

HGF has been implicated in mammalian placental development, based on the evidence that HGF knockout mice exhibit embryonic death in utero because of placental insufficiency.[16] During pregnancy, HGF can be produced by placental villous mesenchymal core. It plays a paracrine role on trophoblasts that express c-Met.[17,18] It has been demonstrated that placental production of HGF is decreased in women who develop complications of preeclampsia or intrauterine growth restriction.[19,20] Considering the contribution of sMet to the tight regulation of angiogenesis and other processes controlled by HGF, we hypothesize that the aberrant circulating level of sMet may be manifested before the onset of the clinical syndrome of preeclampsia.

In this prospective study, we measured the maternal plasma level of sMet at different gestational stages in normal pregnant women and those who later developed severe preeclampsia. The data are further subjected to receiver-operating characteristic (ROC) curve analysis to evaluate the predicting value of sMet level for risk of developing severe preeclampsia.

MATERIALS AND METHODS

Patients

A prospective nested case-control study was conducted in 51 normal pregnant women and 44 patients with severe preeclampsia. The donors were selected from a larger cohort of about 3000 young pregnant women who underwent perinatal medical care at the Department of Obstetrics and Gynaecology, Peking University First Hospital, China, during November 2005 to March 2007.

The study was approved by the Research Ethic Committees of the Institute of Zoology, Chinese Academy of Sciences, and Peking University First Hospital, and informed consents were obtained from all patients.

After delivery, the women were classified as having developed preeclampsia or uncomplicated. Normal or uncomplicated pregnancy was defined as a unifetal gestation in a previously normotensive woman who did not suffer from higher blood pressure and proteinuria during pregnancy and delivered a healthy neonate with a weight adequate for gestational age after 37 weeks of pregnancy.[21] Severe preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy.

In brief, these patients had no history of preexisting or chronic hypertension but showed systolic blood pressure of greater than 160 mm Hg or diastolic blood pressure of greater than 110 mm Hg on at least 2 occasions, accompanied by significant proteinuria (>2 g per 24 hours or ≥3 by dipstick in 2 random samples collected at a >4 hour interval) after 20 weeks of gestation.[1,21]

The patients who developed renal disease, transient hypertension in pregnancy, gestational diabetes, spontaneous abortion, intrauterine fetal death, fetal chromosomal or congenital abnormalities, or pregnancies conceived by fertility treatment were excluded from this study. The clinical characteristics of the patients included in this study were summarized in Table 1.

Plasma samples processing

We collected 2 mL of peripheral blood for each patient during the routine visits at different gestational stages (Table 2). Plasma was harvested, aliquoted, and stored at −80° within 12 hours of blood collection.

Enzyme-linked immunosorbent assay (ELISA) for sMet

Plasma concentration of sMet was determined by specific sandwich ELISA according to the manufacturer's instruction (Parameter; R&D Systems Inc, Minneapolis, MN). Each plasma sample of 0.5 μL was used for assay, and all samples were assayed in duplicate in 1 set of experiment. A standard curve was produced by dilution of the 4000 pg/mL standard to give 7 standard concentrations, and the minimal detectable dose in the assay was 62.5 pg/mL. The concentrations of the samples were determined according to the absorbance of the samples and standards at 450 nm wavelength in a microplate reader.

The ELISA experiments were repeated 3 times. The data with poor duplicate in 1 set of experiments were omitted, and the mean concentration for each sample

was calculated based on the repeated experiments.

Statistical analysis

Statistical analysis was performed with SPSS software for Windows 11.5 (Statistical Package for Social Sciences; SPSS Inc, Chicago IL). Because the data set in this study was not large (n <40) according to the Central Limit Theorem, the Kolmogorov-Smirnov test was used to assess the normality of ELISA data distribution to avoid invalid results that might be produced by the Student *t* test.

For plasma sMet level and clinical characteristics, statistical analysis was performed using analysis of variance, and significant differences between normal pregnant and preeclamptic women were evaluated using Student *t* test. A value of $P < .05$ was considered statistically significant. Threshold values used for risk prediction were determined based on ROC curves, plotting the true positive rate against the false-positive rate (1-specificity) at each cutoff point.

RESULTS

According to the criteria described in *Materials and Methods*, 95 women were enrolled in this study. Of them, 51 were normal pregnant and 44 suffered from severe preeclampsia. There are no significant differences in age, body mass index, glucose tolerance (indicated by 50 g glucose challenge test), infant birthweight, and primiparous percentage between the normal pregnant and the preeclamptic women. However, the systolic and diastolic blood pressures as well as the 24 hour urine protein of the preeclamptic patients are evidently higher than those of the normal ones (Table 1).

Plasma levels of sMet were measured by specific ELISA in these pregnant women at different gestational stages. As shown in Table 2 and Figure 1, mean plasma concentration of sMet changed in a gestation-dependent manner during normal pregnancy. The level was relatively low at gestational weeks 15-18 (259.1 ng/mL), reaching an approximately 1-fold higher peak at weeks 19-24 (498.7 ng/mL).

At weeks 25-30, sMet level decreased to about 1.4-fold of that at weeks 15-18. After weeks 31, it maintained a relatively constant level, which was slightly higher than that at weeks 15-18. In severe preeclamptic patients, mean sMet concentration did not show evident variation along the gestation and was significantly lower than that in the gestational stage-matched controls. At weeks 19-24, mean sMet level in the patients was only 56% of that in the corresponding controls.

We classified the patients into 2 groups: early-onset severe preeclampsia (EOPE) and late onset severe preeclampsia (LOPE), according to whether the clinical manifestations occur before or after the 32nd week of gestation, respectively. In this study, women with EOPE delivered at about 5-10 weeks earlier than those with LOPE, and there was no difference in blood pressure and level of proteinuria between the 2 groups.

The levels of sMet in EOPE and LOPE groups were separately analyzed. As shown in Figure 2, the variation pattern and the level of sMet throughout gestation were similar between the 2 groups (Figure 2). Plasma sMet concentrations in both EOPE and LOPE groups kept at lower levels than the corresponding control from gestational weeks 15 to delivery.

To evaluate the association of plasma sMet with the risk for developing preeclampsia, the data were further analyzed by ROC curves with SPSS software. As shown Figure 3 and Table 3 of the

TABLE 2
Concentration of soluble c-Met in plasma derived from normal pregnant women and women with severe preeclampsia at different gestational stages

	sMet concentration, ng/mL	
Gestational wk	Normal pregnancy	Severe preeclampsia
15-18	259.1 ± 13.3 (n = 22)	182.5 ± 6.8 (n = 19)[a]
19-24	498.7 ± 66.1 (n = 10)	219.1 ± 10.7 (n = 13)[a]
25-30	356.2 ± 18.3 (n = 35)	189.9 ± 9.7 (n = 16)[a]
31-35	298.7 ± 18.9 (n = 25)	225.9 ± 11.1 (n = 14)[a]
≥36	293.7 ± 20.6 (n = 19)	235.1 ± 11.7 (n = 18)[a]

Data are shown in mean ± SEM. Significant difference between groups was analyzed with Student *t* test.

[a] Compared with the gestational stage-matched control ($P < .05$).

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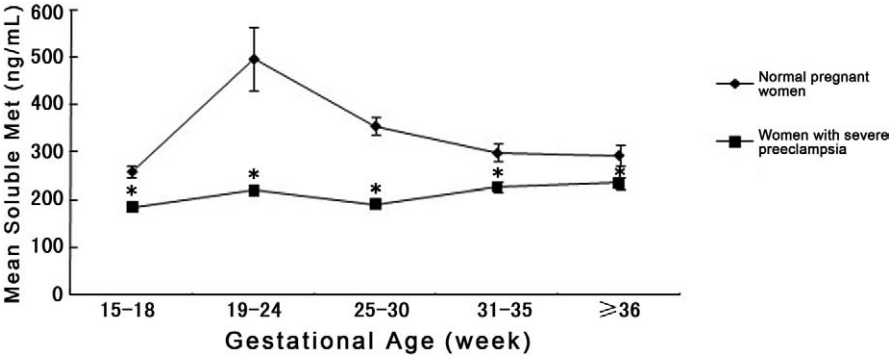
FIGURE 1
Gestational change of soluble c-Met in plasma



Gestational change of soluble c-Met in plasma of normal pregnant women and those with severe preeclampsia. Significant difference between groups was analyzed with Student *t* test. *Asterisk* indicates the comparison with the gestational stage-matched control ($P < .05$).

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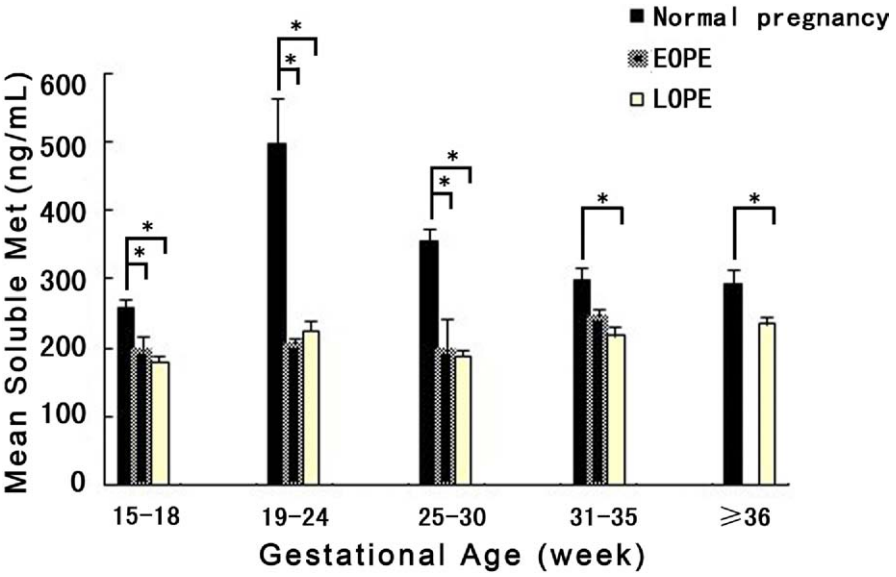
FIGURE 2
Gestational change of plasma soluble c-Met



Gestational change of plasma soluble c-Met in normal pregnant women and those who developed early-onset (EOPE) or late-onset (LOPE) severe preeclampsia. Significant difference between groups was analyzed with Student *t* test. *Asterisk* indicates the comparison with the gestational stage-matched control ($P < .05$).

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ROC report, the higher values of area under the ROC curve, 95% confidence interval and sensitivity indicated the higher reliability and accuracy of the threshold values in discriminating the control and disease groups.

The ROC analysis revealed that decreased sMet concentration in plasma was in tight association with the risk for developing severe preeclampsia, especially at gestational weeks 15-18, 19-24, and 25-30 when the cutoff points were 221.3 ng/mL, 269.2 ng/mL, and 238.4 ng/mL, respectively (Table 3).

COMMENT

The present study revealed a significant correlation between soluble c-Met concentration in maternal plasma and the clinical manifestation of severe preeclampsia. The circulating level of sMet remains at a significantly low level along gestation in the patients who later developed severe preeclampsia, and there are clear cutoff values at different pregnant stages. The ROC curve analysis demonstrated the reliability and accuracy of these threshold values in predicting the clinical risk for severe preeclampsia, especially at gestational weeks' 15-30.

Noticeably, when compared with the gestational age-matched controls, the patients with preeclampsia begin to exhibit an evident decrease of plasma sMet level at early second trimester (weeks 15-18), which is more than 2 months before the onset of the clinical symptoms of hypertension and proteinuria. When taken the onset time into count, we did not find obvious difference in the alteration pattern of sMet between early-onset and late-onset preeclamptic women. In other words, the alteration level and the beginning of the alteration in sMet seemed not dependent on the onset time of severe preeclampsia.

This manner is much different from that of sFlt-1 and sEng, which have been revealed to alter in tight association with the onset time of preeclampsia. Levine et al[22] reported that the increase in the level of sEng as well as the sFlt-1/PlGF ratio began at weeks 17-20 in early-onset preeclampsia (9-11 weeks before the clinical manifestation) but at weeks 25-30 in late-onset preeclampsia (5 weeks before the clinical symptoms). Meanwhile, women with early-onset preeclampsia showed more pronounced alterations in these substances than those with late-onset type.

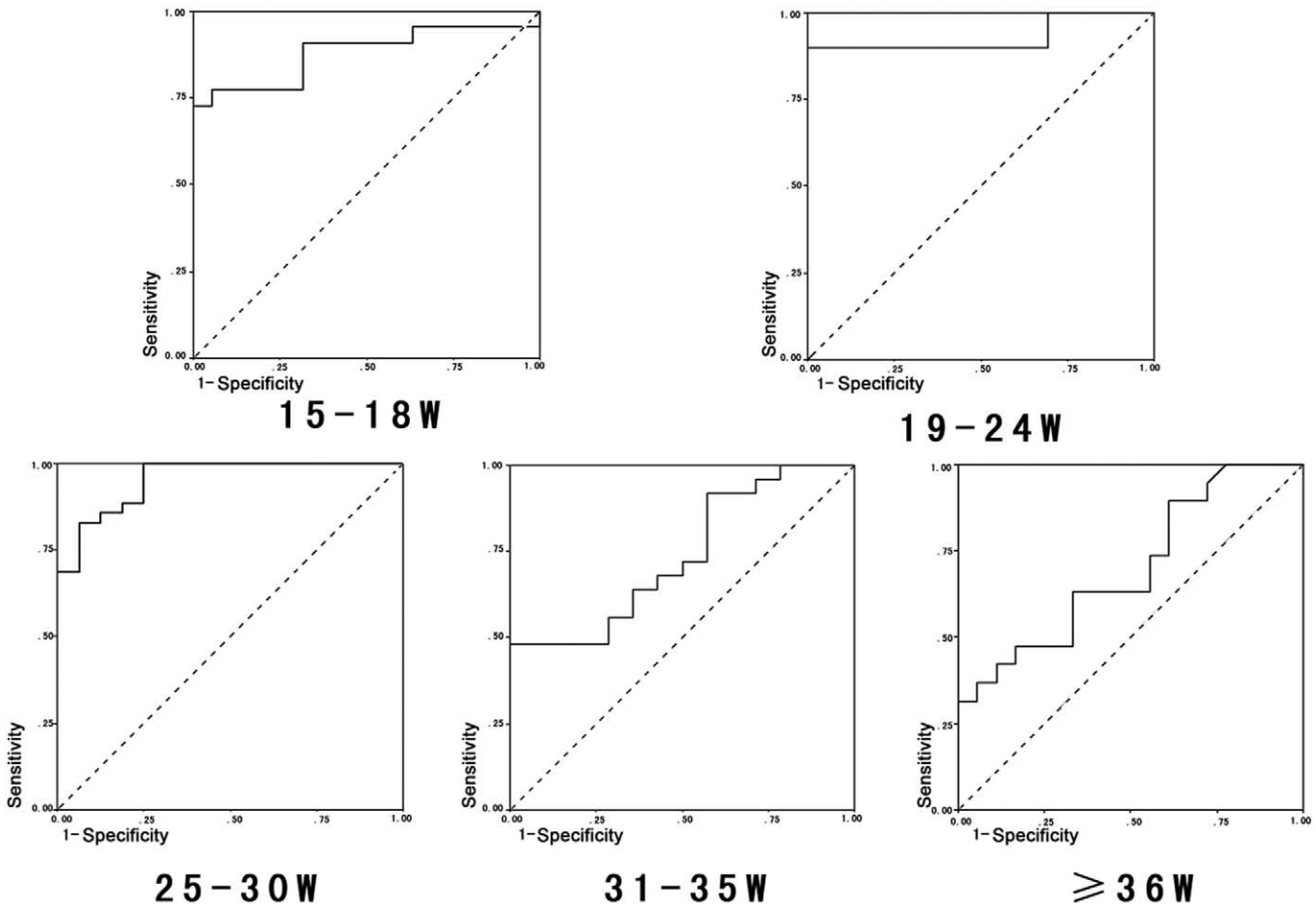
One problem is that we have not yet measured the plasma level of sMet during the first trimester and thus are not sure of the exact beginning time of sMet alteration in preeclamptic patients. However, at present, it is likely that the change of plasma sMet in severe preeclamptic women may precede that of sFlt-1 and sEng and might be a more general risk factor for severe preeclampsia at the early second trimester.

The early change of sMet production in women who later develop preeclampsia seems to indicate the participation of this truncated receptor in pathogenesis of the disease. HGF is known to have motogenic and/or mitogenic activity in smooth muscle cells (SMCs) and endothelial cells. Its function is mediated by the tyrosine kinase receptor, c-Met. Shedding of c-Met from cell membrane has been demonstrated in human SMCs and endothelial cells, and the resulted sMet can bind to HGF at relatively low affinity. On the other hand, sMet may also form inactive heterodimers with membrane receptor and prevent the formation of active homodimer. In these ways, sMet can interrupt HGF/c-Met signaling and may produce an antiantiogenic effect locally or at remote site.

The present study revealed an evident decrease in plasma sMet level in women who later developed severe preeclampsia. Iioka et al[23] reported that circulating level of HGF did not change significantly in preeclamptic patients. Therefore, it seems the homeostasis between HGF and sMet is impaired in preeclamptic women.

Multiple groups have demonstrated that the patients have imbalanced circulating level of angiogenic and antiangiogenic factors compared with normal pregnant ones. The well-understood changes include decreased levels of PlGF and VEGF as well as elevated levels of sFlt-1 and sEng, resulting in reduced angiogenic effects of VEGF/PlGF and subsequent endothelial dysfunctions in preeclamptic patients.[24,25] On the contrary,

FIGURE 3
ROC plots to detect soluble c-Met in plasma



ROC plots were used for the detection of soluble c-Met in plasma derived from normal pregnant women and those with severe preeclampsia at different gestational stages.

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the decreased sMet level in preeclamptic patients seems to facilitate the angiogenic effect of HGF. One possibility might be that the alteration of sMet is the result of some feedback to protect endothelial cells from overinjury.

On the other hand, it has been well known that HGF/c-Met signaling plays important roles in renal cells. HGF can stimulate the growth and enhance the motility of epithelial cells (known as podocytes) and induce renal epithelial

TABLE 3
Report of the ROC analysis for soluble c-Met level in plasma derived from normal pregnant women and women with preeclampsia

Gestational age, wk	Threshold values, ng/mL	Area under the curve	SE	95% CI	Sensitivity, %	Specificity, %	*P* value
15-18	221.3	0.88	0.057	0.768–0.993	95	77	< .001
19-24	269.2	0.931	0.068	0.797–1.064	93	90	< .001
25-30	238.4	0.954	0.027	0.9–1.007	94	83	< .001
31-35	281.4	0.737	0.08	0.58–0.895	100	48	.015
≥36	255.5	0.697	0.086	0.529–0.866	67	63	.045

CI, confidence interval.

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tubule regeneration as well as suppress fibrogenic cytokine expression in myofibroblast cells.[26] HGF can also counteract TGF-β effects to protect peritubular capillaries and glomerular endothelial cells from apoptosis.[27]

It has been revealed that insufficient production of HGF is causative for renal fibrosis. Preeclampsia is associated with a characteristic glomerular lesion, known as glomerular endotheliosis, and proteinuria in women with preeclampsia is likely to be due to direct injury of podocytes. It has been proposed that altered circulating sFlt-1 and sEng may account for renal dysfunctions in preeclamptic women, but the mechanisms remains unclear.[10]

At present, it remains unclear whether there exist interactions between sMet and sFlt-1 or sEng, and we do not know the cause-effect relationship between the declined sMet and endothelial dysfunction or renal failure in the occurrence of preeclampsia. Further extensive studies are needed to determine the significance of this substance in the pathophysiology of preeclampsia.

To reveal the mechanism underlying the alteration of plasma sMet in preeclamptic patients, the source of sMet during pregnancy needs to be determined. Both HGF and c-Met have been detected in human placenta, and c-Met is mainly localized in trophoblasts and endothelial cells.[17,18]

Our preliminary data showed the production of sMet in human placenta tissues as well as the cultured trophoblast cells (Zeng X, Yang Y, Li Y, Li D, Yang H, Wang Y, unpublished data). Wajih et al[15] demonstrated that HGF was able to induce the release of sMet in human endothelial and smooth muscle cells. Therefore, we propose that HGF may be responsible for the production of sMet in human placenta, and this may explain the fact that circulating sMet is the highest at the second trimester of normal pregnancy when placental HGF production also peaks.[19,28] However, this can not give a good explanation for the early alteration in sMet level in preeclamptic patients because the down-regulated mRNA expression as well as the decrease in immunoreactivity of HGF in preeclamptic placenta was observed only at the third trimester.[19]

Apart from the placenta, other organs such as the maternal liver and kidney may contribute to the production of HGF and sMet.[29,30] Change of circulating sMet in women who later develop preeclampsia might reflect the much early malfunctions in these maternal organs.

At present, it is not clear which enzyme(s) is responsible for the shedding of c-Met. Wajih et al[15] demonstrated that release of sMet could be inhibited by the metalloproteinase inhibitor, indicating the involvement of metalloproteinase activity in the shedding process. A Disintegrin and Metalloproteinases (ADAMs) are a family of transmembrane proteins with metalloproteinase activities. Data from Kopitz et al indicated ADAM10 as 1 of the possible sheddases for c-Met.[31] It is not known whether ADAM10 expression is abnormal in placenta or maternal organs in preeclamptic women; however, some studies demonstrated that serum ADAM12 was reduced at the first trimester in the patients.[32,33] Identification of the regulators and enzymes involved in the shedding of c-Met will further our understanding on the physiopathology of preeclampsia.

Our study provides the first evidence that circulating sMet levels are significantly lower at the early second trimester of severe preeclamptic women than healthy pregnant women. This finding raises the exciting possibility that sMet could serve as an early predictive biomarker for severe preeclampsia. Further studies are needed to confirm the functional and therapeutic significances of sMet for preeclampsia. ■

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