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Diagnostic utility of serum levels of various angiogenic peptides in patients with various types of hypertensive disorders during pregnancy

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INTRODUCTION

Hypertensive disease occurs in approximately 12-22% of pregnancies and contribute significantly to maternal and perinatal mortality and morbidity.[1] In 2000, the Working Group of the National High Blood Pressure Education Program (NHBPEP) proposed a classification system based on clinical simplicity to provide guidance to practicing clinicians on management. They classified five types of hypertensive disease: Gestational hypertension, Preeclampsia, Eclampsia, Preeclampsia superimposed on chronic hypertension, Chronic hypertension.[2] Gestational hypertension is defined as systolic BP of at least 140 mmHg and/or a diastolic BP at least 90 mm Hg on at least two occasions at least 6 hours apart after the 20th week of gestation in women known to be normotensive before 20 week's gestation. Blood pressure returns to normal by 12 weeks postpartum. Gestational hypertension is the most frequent cause of hypertension during pregnancy. The rate ranges between 6% and 17% in healthy nuliparous women and between 2% and 4% in multiparous women.[3-6] The rate is further increased in women with previous preeclampsia and in women with multifetal gestation. Some women with gestational hypertension will subsequently progress to preeclampsia. The rate of progression depands on gestational age at time of diagnosis; the rate reaches 50% when gestational hypertension develops before 30 week's gestation.7 In addition, some of these women may have undiagnosed chronic hypertension.

Chronic hypertension is defined as hypertension is present and observable before pregnancy or is diagnosed before the 20th week of gestation or is diagnosed for the first time during pregnancy and that does not resolve postpartum.

Preeclampsia is defined as the appearance of hypertension ($\geq$140/90 mmHg) after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria that is defined as the urinary excretion of $\geq$0.3 g protein in a 24-hour specimen. This proteinuria usually correlate with $\geq$30 mg/dL ($\geq$1+ reading on dipstick) in a random urine determination with no evidence of urinary tract infection. The rate of preeclampsia ranges between 2% and 7% in healthy nulliparous women.[3,4] The rate is substantially higher in women with twin gestation (14%)[8] and those with previous preeclampsia (18%).[6] Preeclampsia is considered severe if one or more of the following criteria is present: Blood pressure of 160 mmHg systolic or higher or 110 mmHg diastolic or higher on two ocasions at least 6 hours apart while the patient is on bed rest.

Proteinuria of 5 g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart. Oliguria of less than 500 mL in 24 hours. Cerebral or visual disturbances, Pulmonary edema or cyanosis, Epigastric or right upper-quadrant pain, Impaired liver function, Thrombocytopenia, Fetal growth restriction.

Eclampsia is defiend as the occurrence in a woman with preeclampsia of seizures that cannot be attributed to other causes.

Preeclampsia superimposed on chronic hypertension is diagnosed with following findings: In women with hypertention and no proteinuria early in pregnancy (<20 weeks' gestation), new-onset proteinuria, defined as the urinary excretion of ≥0.3 g protein in a 24-hour specimen is present. In women with hypertension and proteinuria before 20 weeks'gestation any of the following are seen; -sudden increase in proteinuria,-sudden increase in blood pressure in a woman whose hypertension has previously been well controlled, -thrombocytopenia (platelet count<100,000 cells/mm^3), -increase in alanine aminotransferase or aspartate aminotransferase to abnormal levels.[2,9-11]

Although abnormal placental development, systemic endothelial dysfunction, circulating angiogenic factors have been suggested to pathogenesis of preeclampsia,[12] The etiology of hypertensive disease during pregnancy is unknown.

The clinical course of preeclampsia ranges from mild to severe. The disease proceeds slowly in most cases and may never beyond mild preeclampsia; in other cases, the disease proceeds more rapidly, changing from mild to severe within days or weeks.[13,14]

As major goal in managing preeclampsia is the prevention of maternal and perinatal morbidity and mortality, primarily through delivery, therefore for clinical management preeclampsia should be over diagnosed. Two other hypertensive conditions, Gestational hypertension and Chronic hypertension also lead to confusion to differentiate from mild to severe type of preeclampsia. The impacts of these conditions on mother and fetus are different compare to preeclampsia, so are the management strategies. Therefore correct diagnosis and prediction are very important for management. However, at present, the detection of preeclampsia continues to depend upon increasingly frequent antenatal visits in late pregnancy for blood pressure measurement and urinalysis[10,11] as there is no single screening test that is considered reliable and cost-effective for predicting preeclampsia as early as possible thereby allowing appropriate management.

Recently, evidence from our group and others[14-22] that the syndrome may be initiated by soluble placental factors which enter the maternal circulation and cause maternal endothelial dysfunction as showed by exogenous administration of sFlt-1 in rats caused hypertension, proteinuria and endotheliosis, a pathological renal lesion seen in preeclampsia.[14] Also we have demonstrated that elevated circulating soluble fms-like tyrosine kinase1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), in preeclamptic women at the time of the diagnosis specially 5 wks before onset and significantly decreasing level of spot urinary placental growth factor (PlGF) in women who subsequently developed preeclampsia at 21-32 wks.[13,23] It has also been shown by Levine et al that endoglin, a cell surface receptor for the pro-angiogenic protein TGF-β, is upregulated in preeclamptic placentas and found increased level of endoglin before onset of clinical disease which led to the conclusion that endoglin may synergize with sFlt-1 to cause endothelial dysfunction.[24] All these findings suggest the importance of a circulating anti-angiogenic state in the pathogenesis of preeclampsia. It is conceivable from the findings and data from our group that the antiangiogenic molecule may serve as diagnostic markers in patient at high risk for developing preeclampsia in the future.

We hypothesized that these anti-angiogenic molecule could be utilize in diagnosis of preeclampsia and thus differentiating from other hypertensive diseases like gestational hypertension and chronic hypertension during pregnancy. To test this

hypothesis, here in this manuscript we demonstrate in a pilot study the utility of the anti- angiogenic molecule in different types of hypertensive disorder in pregnancy.

Study Design

We conducted a case-control study analyzing serum levels of sFlt-1 and sEng in women who presented to Labor and Delivery at St. Mary's Hospital with various hypertensive diseases of pregnancy using an enzyme-linked immunosorbent assay (ELISA). The patients were categorized into one of the three following groups based on the National Working Group in Hypertension criteria: Gestational hypertension (n=17), chronic hypertension (n=19) and preeclampsia (n=19). We used women without hypertension or proteinuria as controls (n=20). We analyzed the data using student t-test and ROC curve. We calculated the sensitivity (sens), specificity (spec), and positive and negative likelihood ratio (PLR and NLR) of each peptide in diagnosing preeclampsia from other forms of hypertensive diseases.

Results

The serum sFlt-1 level of 23.5 ng/ml had the best sens (90%) and spec (90%) with the highest PLR (9.0) and the lowest NLR (0.12) in differentiating women with preeclampsia from normal pregnancy. For differentiating those with gestational hypertension, the serum level of 41.8ng/ml had the highest sens (79%) and spec (88%) with the PLR and NLR of 6.7 and 0.24, respectively. For women with chronic hypertension, the serum level of 35.8 ng/ml showed the best sens (84%) and spec (95%) with PLR of 16 and NLR of 0.17. For sEng, the serum level of 24.8 ng/ml, had 90% sens and 95% spec with PLR of 18 and NLR of 0.11 in differentiating women with preeclampsia from those with normal pregnancy. For women with gestational hypertension, the serum sEng level of 33 ng/ml had the highest sens (84%) and spec (88%) with PLR of 7.2 and NLR of 0.18. For women with chronic hypertension, the serum level of 31.5ng/ml had sens of 79% and spec of 99% with PLR of 4 and NLR of 0.2.

Conclusion

Serum levels of both sFlt-1 and sEng may be useful in differentiating patients with preeclampsia from those with gestational and chronic hypertension.

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