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RESEARCH ARTICLE

Soluble Endoglin as a new marker for prediction of pre-eclampsia in early pregnancy

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Abstract *Objective:* To evaluate the use of a new marker in the prediction of pre-eclampsia few months before the onset of manifestations.
Materials and methods: Sixty-six women during early pregnancy were enrolled in the present study and were divided as follows: Thirty-three pregnant women: 15 developed gestational hypertension and 18 pregnant women who later developed pre-eclampsia and 33 normotensive pregnant women taken as controls. Exclusion was done to twin pregnancies, cases with fetal abnormalities, maternal renal disease and connective tissue diseases. Serum concentration of angiogenic markers (VEGF, PIGF) and anti-angiogenic marker: soluble Endoglin (sEng) was measured during 14–18 weeks gestation using ELISA technique. All women were followed up till delivery.
Results: A statistically significant difference was found in comparing the median level of VEGF and PIGF in cases of gestational hypertension and pre-eclampsia with controls ($P < 0.0005$ and $P < 0.0005$). A statistically significant difference was found in comparing the median level of VEGF in gestational hypertension group with pre-eclampsia ($P = 0.19$). The median level of soluble Endoglin had a statistically significant difference in comparing gestational hypertension and pre-eclampsia group with controls ($P < 0.0005$). A cut-off value of 31 pg/ml VEGF yielded

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a sensitivity of 94.4%, specificity of 72.9% with accuracy 78.8%. PIGF at cut-off level of 49 pg/ml had a sensitivity of 77.8, specificity of 89.6% with accuracy 86.6%. In case of sEng the sensitivity was 94.4%, specificity was 87.5% and accuracy was 89.5%.

Conclusion: Pregnant women who are at risk of developing pre-eclampsia can be offered measuring these markers as a screening method to point out those who are more likely to develop pre-eclampsia and warrant close observation and intervention.

1. Introduction

Pre-eclampsia is a pregnancy-specific multisystem disorder characterized by development of hypertension and proteinuria after 20 weeks gestation (1). Accurate prediction of pre-eclampsia is crucial to allow judicious allocation of resources for monitoring and preventive treatment to improve maternal and perinatal outcomes.

In Egypt, according to the Egyptian National Maternal Mortality Study (2000), poor quality antenatal care contributed to 15% of maternal deaths, 34% of them are associated with hypertensive disorders with an estimated 13 maternal death per 100,000 live births. The ministry of Health and Population survey showed that 13% of maternal mortality is due to hypertensive disease with pregnancy (2).

Despite intensive research, the etiology of pre-eclampsia remains unknown. Current hypotheses include vascular-mediated factors, placental ischemia, genetic predisposition and immune mal-adaptation, all of which have been stated to contribute to the development of pre-eclampsia (3).

Biochemical markers that could predict the subsequent onset of pre-eclampsia before maternal clinical manifestations become apparent would be advantageous because they may elucidate the patho-physiologic mechanisms of the disorder and identify specific patients early in pregnancy that are at high risk for developing pre-eclampsia. If the application of such simple tests is possible in the future they can be very useful especially in developing countries (4).

Vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) are important mediators of angiogenesis, prominently expressed in the placenta (5). Some researchers reported that serum VEGF concentration is significantly lower in pregnant women and even further reduced in pre-eclampsia (6,7). Serum PLGF in the early trimester was associated with subsequent occurrence of pre-eclampsia (8).

Another cytokine has also been implicated in the etiology of pre-eclampsia, Endoglin (Eng), also called CD105, which is a homodimeric transmembrane glycoprotein primarily associated with human endometrium (9). Placental Endoglin is over expressed in pre-eclampsia, releasing soluble Endoglin into the maternal circulation that correlates with disease severity and falls after delivery (10). It was also found to be elevated two to three months before the manifestations of pre-eclampsia start to appear, so it can be a potential predictor of pre-eclampsia (11). The aim of the present study is to evaluate the use of a new marker in the prediction of pre-eclampsia few months before the onset of manifestations.

2. Materials and methods

This longitudinal case-control study included all pregnant women with previous history of pregnancy-induced hypertension attending antenatal care between June 2006 and January 2007. Approval of the ethics committee was obtained, and all participants signed informed consents. Blood samples were taken between 14 and 18 weeks gestation. Follow-up of these women was done till delivery. Those who completed their follow-up were enrolled in the present study. A total of 66 singleton pregnant women between 18 and 35 years old were divided as follows: 15 pregnant females who developed gestational hypertension, 18 pregnant women who later developed pre-eclampsia and 33 normotensive pregnant women taken as controls.

All women were asked to be sure of their last menstrual period (LMP) and confirmed by ultrasonography done for all pregnant women as part of routine follow-up and to determine gestational age. All women were subjected to full history taking, general examination and blood pressure measurement.

Gestational hypertension was considered in the elevation of blood pressure after 20 weeks gestation to $\geqslant$140 mm Hg systolic and/or $\geqslant$90 mm Hg diastolic. For pre-eclampsia elevated blood pressure was accompanied with proteinuria measured by dipstick as at least 1 + (30 mg/dl). Severe pre-eclampsia was considered if diastolic blood pressure was at least 110 mm Hg. Exclusion was done to twin pregnancies, cases with fetal abnormalities, maternal renal disease and connective tissue diseases.

Sample collection: five milliliter blood samples were collected from pregnant females at 14–18 weeks gestation. The samples were collected on EDTA as an anticoagulant and then centrifuged at 1000 rpm for 10 min. Plasma was divided into aliquots and frozen at −70 °C till assay time. Routine investigations were done, in addition plasma angiogenic markers were assayed, and vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and soluble Endoglin (sEng) were quantified with an enzyme-linked immunosorbent assay kit (R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN 55413, USA) *(12).

2.1. Statistical analysis

Data are presented as mean and standard deviation and compared between two groups using *t*-test and more than two groups using analysis of variance (ANOVA). Quantitative data were compared using spearman correlation coefficient (rs). The optimal cut-off for different analyte was calculated by constructing a receiver-operating characteristic (ROC) curve and odds ratio were calculated for each parameter at the selected cut-off value. *P* value less than 0.05 was considered