The Study of Diagnostic Value of Placental Growth Factor for Predicting Pre-eclampsia in the First Trimester of Pregnancy

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Abstract **Background**: Preeclampsia is the most common pregnancy problems which are characterized by hypertension and proteinuria. This status can be further complicated by eclamptic seizures. Preeclampsia is among the leading causes of mortality in mothers, fetuses and newborns around the world. The exact mechanism causing preeclampsia has much been controversial and has not yet fully known. The current study sought to identify the diagnostic value of changes in the serum levels of placental growth factor in predicting the occurrence of preeclampsia. **Materials and Methods**: Serum samples were taken from 700 mothers who were between 8 to 12 weeks of pregnancy. Placental growth factor levels were compared and examined in 35 healthy pregnant women and 35 pregnant women with preeclampsia who were randomly selected. **Results**: Serum concentration of placental growth factor had a significant difference between healthy pregnant women and pregnant women with preeclampsia ($P<0.05$). Based on the results of the present study, placental growth factor has 57% sensitivity, 77% specificity, 71% positive predictive power and 64% negative predictive power in predicting the occurrence of preeclampsia. **Conclusion**: Serum levels of placental growth factor in the first trimester of pregnancy can be used to predict the occurrence of preeclampsia.

Keywords: preeclampsia, placental growth factor, predict

1. Introduction

Preeclampsia is a major complication of pregnancy that can lead to serious clinical challenges [1,2]. Prevalence rate of preeclampsia has been reported 5 to 15% [1,3]. Preeclampsia is defined as hypertension over 140/90 mmHg which is associated with proteinuria. This disease is a leading cause of maternal and neonatal mortality, especially in developing countries [4,5]. Predicting the occurrence of preeclampsia and its early diagnosis require a careful obstetrical care, therefore; predictive methods of preeclampsia are of great importance [6]. Among the methods used to predict the occurrence of preeclampsia should note to roll (Rot) test [1], measurement of homocysteine [6,7], assessing changes in testosterone [8,9], assessing CRP and other inflammatory indicators [10], checking hematocrit levels [11,12], measurement of calcium ratio to urinary creatinine [13,14] and 24-hour urinary calcium excretion [15]. Among these mentioned methods, each of which is a subject of various debates and sometimes conflicting, placental growth factor has been analyzed and interpreted in several studies as well. The current study aims to determine diagnosis value of placental growth factor for predicting the occurrence of preeclampsia in the first trimester of pregnancy.

2. Materials and Methods

The present study is designed to evaluate the diagnostic value of placental growth factor in predicting the occurrence of preeclampsia. All pregnant women attending prenatal clinic of Shahid Akbar Abadi and Firouzgar hospital, randomly entered the study in a one-year period from 2012 to 2013, in case of having specified inclusion criteria. Inclusion criteria include being in the first trimester of pregnancy (up to 12 weeks), maternal age between 15 to 35 years, singleton pregnancy, no history of chronic hypertension or gestational diabetes during pregnancy and also lack of kidney problems in the current pregnancy. Exclusion criteria of patients were lack of consent for participating in the study, lack of consent to continue the study at any point, lack of consent to Follow-up, fetal death and maternal death before diagnosis of preeclampsia.

All patients were fully apprised of the different stages of the study and in case of having consent were enrolled in the study. Informed consent was obtained from all patients.

This study imposes no diagnostic or invasive therapeutic procedure on patients. Also, to measure the serum level of placental growth factor no additional cost was taken from the patients. Patients' information remained confidential in this study. The current study was approved by the ethics committee of Tehran University of Medical Sciences and Health Services. Simple Random sampling method was used. In the next phase, all pregnant patients were regularly followed-up on the basis of common patterns of pregnant mothers. At each visit, diagnostic measures were done for early detection of preeclampsia. Also, appropriate sample serum was taken in the first trimester from all pregnant mothers to measure the placental growth factor levels. It is worth mentioning that blood samples were stored at temperature -20ċ. Measurement of placental growth factor levels took place at the end of the study through ELISA method using specific kits purchased by the researchers involved in the project. According to the results obtained by previous studies, the sample size was 35 patients. Therefore, out of 700 under study women, 35 pregnant women with preeclampsia and 35 healthy pregnant women were randomly selected for the study.

Collected data from patients (interviews and patients' history, physical examination and laboratory evaluations including serum levels of placental growth factor) were recorded in a specific designed form. These collected data were examined using the SPSS$_{18}$ software, descriptive statistical parameters such as mean, median and measures of scattering like standard deviation. P-value < 0.05 was considered as significant level. In addition to the above parameters in the present study, sensitivity, specificity, positive and negative predictive value of the serum levels of placental growth factor were examined for predicting the occurrence of preeclampsia in the later stages of pregnancy. Due to the obtained results from previous efforts, serum level of this factor in women who develop preeclampsia later in pregnancy would be less than normal women. In the current study, serum level of 42 was intended as cut off point on the basis of results of other studies. With a diagnosis of preeclampsia, all patients were typically treated according to the existing standards and conducting the study did not cause a delay in treatment.

3. Results

The mean age of 35 healthy pregnant women was 25.71 years with a standard deviation of 4.73. Among 35 pre eclamptic pregnant women, the mean age and standard deviation were 24.83 and 5.26, respectively. Statistical tests found no significant differences in age distribution of these two groups (P>0.05).

The mean weight of healthy pregnant women was 60.45 kg with standard deviation of 8.30. Preeclamptic pregnant women had a mean weight of 63.37 kg and standard deviation of 11.76. Statistical tests found no significant differences in mean weight of these two groups (P>0.05).

The BMI mean and standard deviation of healthy pregnant women were 23.05 and 2.59. These figures were 24.46 and 4.53 in preeclamptic pregnant women. No significant differences were found in BMI mean of these two groups (P>0.05).

The mean number of pregnancies in healthy pregnant women was 1.62 and in the patient group this number was 2.11. But, Statistical tests showed no significant differences in mean number of pregnancies in these two groups (P>0.05).

In healthy pregnant group, 7 patients (20%) once had a previous history of abortion, while in group of patients with preeclampsia; 3 patients (8.6%) experienced an abortion, another 3 patients (8.6%) had two abortion histories and 1 patient (2.9%) had a history of three previous abortions. A significant difference was seen in abortion prevalence of these two groups (P>0.05).

The mean age of the infants at birth in healthy pregnant women was 38.85 weeks and in preeclamptic pregnant women was 34.5 weeks. Statistical tests showed a significant difference in mean age of the infants at birth in these two groups (P<0.05).

Serum levels of placental growth factor were examined in the current study among pregnant women in the first trimester of pregnancy. The serum level mean of placental growth factor was 54.37 with a standard deviation of 14.86 in healthy pregnant women. The serum level mean of this indicator in patients with preeclampsia was 39.02 with a standard deviation of 13.13. Statistical tests showed a significant difference in serum level mean of placental growth factor in these two groups (P<0.05).

Data related to Serum levels of placental growth factor are summarized in Table 1. Based on the results, placental growth factor has 57% sensitivity, 77% specificity, 71% positive predictive power and 64% negative predictive power in predicting the occurrence of preeclampsia.

Table 1. The mean, SD and P-value of variables

Variable	Group	Mean	SD	P-value
Age	Healthy pregnant women	25.71	4.73	P>0.05
	Preeclamptic pregnant women	24.83	5.26	
Weight	Healthy pregnant women	60.45	8.30	P>0.05
	Preeclamptic pregnant women	63.37	11.76	
BMI	Healthy pregnant women	23.05	2.59	P>0.05
	Preeclamptic pregnant women	24.46	4.53	
Number of pregnancies	Healthy pregnant women	1.62	2.11	P>0.05
	Preeclamptic pregnant women	1.81	2.15	
Previous history of abortion	Healthy pregnant women	0.20	1.03	P>0.05
	Preeclamptic pregnant women	0.86	1.23	
The mean age of the instants	Healthy pregnant women	38.85	4.96	P>0.05
	Preeclamptic pregnant women	34.5	5.29	
Serum levels of placental growth factor	Healthy pregnant women	54.37	14.86	P<0.05
	Preeclamptic pregnant women	39.02	13.13	

Table 2. Findings related to placental growth factor serum levels in predicting preeclampsia

	Occurrence of Preeclampsia in Pregnancy	Non-occurrence of Preeclampsia in Pregnancy
Placental growth factor confirming the occurrence of preeclampsia	20	8
Placental growth factor confirming the non-occurrence of preeclampsia	15	27

4. Discussion

Many studies have been done on the predictive value of various indicators of preeclampsia occurrence in different communities and races [8]. Inconsistent results may be due to the differences in sample size, prevalence of preeclampsia, materials and methods and the race of study population [4,5,6,7,8]. The current study aims to determine diagnosis value of placental growth factor for predicting the occurrence of preeclampsia in the first trimester of pregnancy. Among the several predictive methods of preeclampsia occurrence, each of which is a subject of various debates and sometimes conflicting, placental growth factor has been analyzed and interpreted in various studies as well. In addition to the epidemiological evaluation and prominent role of the preeclampsia around the world in maternal and neonatal mortality, Bdolah and colleagues explored the possible mechanisms causing these pathological deals. According to this study, imbalance between angiogenic factors plays an important role in creating the disease. For example, one of the key molecules that its concentration disturbance may cause preeclampsia is placental growth factor. PIGF is a molecule with pro-angiogenic properties similar to that of VEGF (Vascular Endothelial Growth Factor). Both of these molecules are inhibited by Fms-like tyrosine kinase1 (SFIt1) molecule. Imbalance of these three molecules plays a key role in the occurrence of preeclampsia and existence of a balance in them properly lead to invasion of cytotrophoblasts. Otherwise, symptoms of preeclampsia will appear [17]. Baumann and colleagues also explored the importance of preeclampsia in their study to evaluate the new four indicators in the diagnosis of preeclampsia. This evaluation is due to the importance of this disease and the inefficiency and contradictory results of previous indicators. Based on the findings of this study, Fms-like tyrosine kinase1 (SFIt1), PIGF (Placental growth factor), PP-13 (Placental protein-13) and SEng (Soluble endoglin) have a high predictive value for predicting the occurrence of preeclampsia in the later stages of pregnancy. This value is doubled when combined with Doppler Ultrasound in the first trimester of pregnancy. In the study of Devivo and colleagues, PIGF, Endoglin and SFIt1 indicators were compared in two groups of 52 healthy pregnant women and 52 preeclamptic pregnant women. In all three of these factors, a significant difference was observed between the 24th and 28th week of pregnancy which confirms the usefulness of these three factors in the prediction of preeclampsia [18]. Indicator of $\frac{SFIt-1}{PIGF}$ is presented as the most accurate method of prediction [19]. In Wikstrom and colleagues study, SFIt-1 and PIGF levels of two preeclamptic patient groups with early onset (before 32nd week of gestation) and with delayed onset (after 35th week of gestation) were compared. Based on the obtained results, both SFIt-1 and PIGF indicator levels increased significantly in both groups of patients, but the increase was more significant in patients with preeclampsia. This study recommends the widespread use of these indicators in early detection of preeclampsia [20].

Stephan and colleagues combined Doppler Ultrasound and angiogenic factors such as SFIt-1 and PIGF in the first trimester of pregnancy to predict the subsequent risks. On the basis of obtained findings, combination of these two indicators, SFIt-1 and PIGF, has 83% sensitivity and 95% specificity for predicting the early occurrence of preeclampsia [20]. All pregnant women attending prenatal clinic of Shahid Akbar Abadi and Firouzgar hospital, randomly entered the study in a one-year period from 2012 to 2013, in case of having the required inclusion criteria. Data related to serum levels of placental growth factor are summarized in Table 1. Considering the results of Table 1, placental growth factor has 57% sensitivity, 77% specificity, 71% positive predictive power and 64% negative predictive power in predicting the occurrence of preeclampsia. This is in line with results of Baumann [18], Devivo [19] and Wikstrom [20] studies, angiogenic factors but it is significantly lower than the Stephan study results [20]. In the study of Stephan and colleagues [20], Doppler Ultrasound is used along with angiogenic factors in the first trimester to predict the risks of preeclampsia occurrence later in the pregnancy. This is the main reason for achieving a high diagnostic value by this study. Studies in which several factors (SFIt-1, PIGF, Endoglin) have been used to predict the occurrence of preeclampsia, early detection is performed with more power [19]. In the current study, serum levels of placental growth factor among healthy pregnant women was 54.37 with standard deviation of 14.86, while the mean level of this factor among preeclamptic pregnant women was 39.02 with standard deviation of 13.13. Statistical tests found no significant differences in mean weight of these two groups (P>0.05). These findings appear to be quite consistent with the findings of other studies [16,17,18,19]. Due to the importance of preeclampsia, several studies have been conducted on the risk factors of it and factors such as nulliparity, age, race, genetic, environmental factors like living at high altitudes, obesity, poverty, chronic hypertension and multiple pregnancies are known to be involved in it. In some other studies, working mothers, a sister with a history of preeclampsia, urinary tract infection during pregnancy, low maternal education, being exposed to Diethylstilbestrol in the uterus, long distance with the previous pregnancy, preterm delivery and IUGR, inadequate prenatal care, season, blood group, maternal low birth weight and smoking have been identified as risk factors [20]. In the present study, no significant differences have been found between healthy pregnant women and preeclamptic pregnant women in term of age, weight, BMI and number of previous pregnancies (p>0.05), whereas the history of previous abortion was significantly greater in pregnant women with preeclampsia (p<0.05).

Lack of difference in parameters like age, weight, BMI and number of previous pregnancies in these two groups is justifiable according to the small sample size. To judge the presence and absence of an obvious role of the mentioned risk factors in the previous Iranian studies, broader researches are needed.

5. Conclusion

Based on the findings of this study and the diagnostic accuracy of placental growth factor, using this test is proposed to predict the occurrence of preeclampsia. Also, extensive researches with larger sample sizes about this indicator and other angiogenic substances (such as SFIt-1, PP-13, VEGF and SEng) are recommended.

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