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Original Research Article

Evaluation of Insulin-Like Growth Factor-I (IGF-I) as a Predictor of Preeclampsia

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Abstract: ***Introduction****:* Preeclampsia (PE) is a serious pregnancy-induced disease characterized by hypertension, proteinuria and other systemic disorders after 20 weeks of gestation and is a leading cause of maternal and fetal morbidity and mortality. The main pathological characteristics of preeclampsia are poor trophoblast cell invasion and uterine spiral artery remodeling dysfunction caused by placenta ischemia and oxidative stress. Nowadays, preeclampsia is considered to be the results of the interactions of genetic and environmental factors. However, its accurate pathogenesis remains unknown. It was considered IGF-1 might be involved in the pathogenesis of preeclampsia. As is known, the behaviors of cells, the formation of placenta and the growth of fetus are widely regulated by insulin-like growth factor 1 (IGF-1). Several studies have shown that IGF-1 was significantly reduced in preeclampsia. ***Objectives***: To assess the role of Insulin like Growth Factor-I (IGF-I) as a Predictor of Preeclampsia. ***Materials and Methods***: It was a prospective cohort study conducted in General Obstetrics and Gynaecology Unit OPD, Dhaka Medical College Hospital from January, 2020 to December, 2020. Pregnant women between 8 weeks to 15 weeks were enrolled for study after fulfilling selection criteria. Serum concentration of Insulin like growth factor-I (IGF-I) was assessed with cut off value of IGF-I 175.9 ng/ml. The value above 175.9 ng/ml was categorized as normal IGF-I and value below 175.9 ng/ml was categorized as low IGF-I. The patients who had value above 175.9 ng/ml were grouped as A. The value below 175.9 ng/ml was grouped as B. Then they were followed up monthly upto 28 weeks, two weekly upto 36 weeks, weekly upto delivery and puerperium for development of preeclampsia or not. All information was recorded in data collection sheet. Data were analyzed by SPSS-23. Data were compared and correlated among groups and presented by tables and figures. ***Result***: Maternal serum concentration of IGF-I was measured in ng/ml between 8 weeks to 15 weeks of gestation and cut off value was estimated as 175.9 ng/ml by Youden Index. The ROC curve of serum IGF-I showed that area under curve (AUC) of serum IGF-I was 0.801 (lower bound 0.614 and upper bound 0.988) in prediction of preeclampsia (P value was 0.011 with 95% confidence interval). Seven patients developed preeclampsia among them 5 patients (45.45%) was in Group-B and 2 patients (4.76%) was in Group-A in Chi-square value. This association showed preeclampsia was significantly higher among study subjects in Group-B with p value 0.003.The sensitivity of serum IGF1 was 71.4%, specificity was 87.0%, positive predictive value (PPV) was 47.5% and negative predictive value was 95.2%. Accuracy of serum IGF1 was 84.9%. ***Conclusion:*** The values of IGF1 were found low in Preeclampsia patients than normal pregnancy. Association between development of Preeclampsia and concentration of IGF-I was significant. Relative risk of development of Preeclampsia increases when concentration of IGF-I was lower than normal in early pregnancy.

Keywords: Insulin -Like Growth Factor-I (IGF-I), Preeclampsia.

INTRODUCTION

Preeclampsia is a multisystem progressive disorder characterized by new onset of hypertension and proteinuria or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of pregnancy [1, 2]. It complicates approximately ~5% of first pregnancies [3] and a major cause of perinatal morbidity and mortality. Although the pathophysiologic process of preeclampsia is not fully elucidated, abnormal placentation, shallow endovascular invasion, placental hypoxia, maternal insulin resistance and diffuse endothelial dysfunction seem to be interconnected key events that may precede

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the clinical onset of the disease by weeks or months. In particular, impaired placental perfusion is evident even from the first trimester as it has been documented by the findings of both histologic and Doppler ultrasound findings of the uterine arteries and the altered levels of placental derived biochemical markers as pregnancy-associated plasma protein (PAPP-A) [4, 5]. Results of previous study indicate that circulating IGF-I levels in both maternal and umbilical cord compartments are low in preeclampsia [6].

The precise origin of preeclampsia remains elusive, but it is believed to be likely multifactorial. A long standing hypothesis has been that preeclampsia develops as a consequence of some kind of immune maladaptation between the mother and the fetus during the very first weeks of pregnancy, leading to a 2-step disorder progression that can be summarized as following: in a first – asymptomatic–step, local aberrant fetomaternal immune interactions within the uterine wall lead to impaired tissue and arterial invasion by trophoblast cells [3]. This results in failed transformation of the uterine spiral arteries and subsequently worsened placental perfusion.

The insulin-like growth factor (IGF) system comprises the IGF peptides (IGF-I, IGF-II), the cellular IGF receptors (type I, type II), and a family of soluble high affinity IGF binding proteins (IGFBP-1 to IGFBP-6) which modulate the bioavailability and activity of the IGFs [7, 8]. Since the discovery of the IGF system before 50 or so years, there is ample evidence for their role in cell proliferation, differentiation and migration and their anti-apoptotic properties as well; thus they are involved in several physiological and pathological processes during prenatal and postnatal life.

During pregnancy, several alterations are noted regarding the expression pattern and function of IGFs. According to a recent study, the maternal serum levels of IGFI remain stable until 20 weeks and then increase whereas IGF-II values do not relatively change throughout gestation. An increase in IGF-I from the first to second trimester was associated with higher risk of preterm preeclampsia. Low concentrations of IGFBP-1, both in the first and in the second trimesters, were related to higher risk of term preeclampsia and moderately increased risk of preterm preeclampsia [9]. Though in non-pregnant-individuals, IGF-I is primarily derived from the liver, during gestation its main source is decidua under the stimulatory action of a specific growth hormone placental variant (PGH) that is produced by syncytiotrophoblast and extravillous trophoblast from the 7^{th} or 8^{th} week of gestation and gradually replaces pituitary growth hormone (GH) in the maternal circulation. PGH is implicated in the physiological adjustment to gestation by stimulating gluconeogenesis, lipolysis and anabolism and exercises its effects either indirectly by regulating IGF-I levels or in an autocrine/paracrine manner [10].

In plasma during postnatal life, most of the IGFs exist in a 140-k Da heterotrimeric complex consisting of IGFBP-3 and an -85 kDa protein, the acid-labile (ALS); when this complex dissociates, IGFs form smaller, binary complexes with the other IGFBPs. The complexity of the IGFBP system in biological fluids is shown by the presence of six IGFBPs, multiple IGFBP proteases, and the intricate regulation of IGFBPs and IGFBP proteases during various physiological and pathophysiological situations. Although the finding that tissue fluids are enriched with one or more of the IGFBPs suggests a role for the IGFBPs in modulating the actions of IGFs in a tissue-specific manner, the exact roles of the IGFBPs in biological fluids are still poorly understood [11]. In the previous study, the findings showed a significant reduction of IGF-1 in preeclamptic placentas and hypoxic trophoblasts, and a remarkable hypermethylation of IGF-1 promoter region in preeclamptic placentas [12].

A central feature of preeclampsia is defective placentation expressed as shallow placental invasion limited to the superficial portion of decidua and abnormal remodeling of the endometrial vasculature due to failure of the conversion of the maternal spiral arteries into vessels of low resistance and high capacitance, as it has been supported by histological analysis of preeclamptic tissue specimens [13]. Indirect evidence for impaired placental perfusion in pregnancies destined to develop preeclampsia has been provided by Doppler studies of the uterine arteries which showed increased pulsatility index (PI) from the first trimester of pregnancy [5, 14]. IGF axis appears to be involved in many aspects of placental development and metabolism both in uncomplicated and preeclamptic pregnancies though the exact signaling pathways have yet to be determined [15]. Studies based on cultured human trophoblast cells and cell lines propose that IGFs promote proliferation, regulate trophoblast migration and the differentiation of cytotrophoblasts into syncytiotrophoblasts and extravillous cells, enhance the proliferation and survival of placental fibroblast, exhibit anti-apoptotic effect and mediate nutrient availability at the fetoplacental unit. Patterns of expression of IGF-II and IGFBP-1 at the decidual- trophoblast interface suggest paracrine interactions occur between the IGF II-expressing invading cytotrophoblast and maternal decidua-derived IGFBP-1. Autocrine/paracrine actions of trophoblast-derived IGFII may be important in invasion, and for both trophoblast and decidual function [16]. Alteration of these factors leads to preeclampsia and other pathological condition during pregnancy.

MATERIALS & METHODS

This prospective cohort study was carried out in the Dept. of Obstetrics and Gynecology, DMCH for a period of 12 month. Total 53 women attended in the Department routinely for ANC between 8 weeks to 15 weeks of gestation were included in the study. Subjects

with multiple pregnancies, prior or current history of hypertension and preeclampsia, patient with co-morbidity like anemia, obesity, thyrotoxicosis, diabetes mellitus, renal disorder, congenital and acquired heart diseases, etc were excluded from study. Ethical clearance was taken from Institutional Review Board of DMCH to conduct this study. After selecting patients 3 cc of blood sample was collected through venipuncture in the cubital vein and taken in a sterile vacuum container. With proper labelling blood samples were sent to laboratory of clinical pathology Department of DMCH. The blood was allowed to clot at room temperature for 30 minutes. The serum was separated by centrifugation. Then the serum was taken in an eppendorf (a small container for taking serum) and labelled. Specimens were stored at -20^{o} C for some time before assay. Assay of the level of IGF-I was done by ELISA kit/ Chemiluminescent Enzyme Immunoassay as per schedule. Results of IGF-I was given as ng/ml (nanogram/ml) and recorded. Cut off value of IGF-I was determined 175.9 ng/ml. The value above 175.9 ng/ml was categorized as normal IGF-I and value below 175.9ng/ml was categorized as low IGF-I. The participants were grouped into two groups. Those who had normal IGF-I (IGF-I>175.9 ng/ml) were grouped as A, those who had low level of IGF-I (IGF-I<175.9 ng/ml) was grouped as B. Then they were followed up monthly up to 28 weeks, two weekly up to 36 weeks and weekly till delivery and upto postpartum for detection of preeclampsia or not. At each visit they were clinically evaluated by measuring blood pressure and heat coagulation of urine for protein if blood pressure was raised. Preeclampsia was diagnosed when blood pressure was found ≥140/90 mm of Hg and proteinuria in heat coagulation test. Then quantification of proteinuria was done by measuring 24-hour urinary protein. A value of >300mg protein in a 24 hour urine collection was diagnostic. The value of IGF-I in two groups was compared with development of preeclampsia or not. All data were analyzed by SPSS 16. Data and results were presented by tables and figures.

RESULTS

According to the questionnaire, history of all the 53 selected cases were taken, the clinical examination was carried out meticulously. Result shows in Group A Mean ± SD of age was 26.28 ± 6.07 years and Group B Mean ± SD of age was 24.28 ± 6.57 years. In Group A 25 (59.52%) patients were primi gravida and 17 (40.47%) patients were multi gravida and in Group B 7 (63.63%) patients were primi gravida and 4 (36.36%) were multi gravida. Difference was not significant (Table 1).

Table 2 shows the association of preeclampsia with serum IGF-I at cut off value 175.9 ng/ml. In Group A (Normal IGF-I) normal pregnancy was 40 (95.23%) and preeclampsia was 2(4.76%). In Group B (Low IGF-I) normal pregnancy was 06 (54.54%) and preeclampsia was 05 (45.45%). So, preeclampsia was significantly higher 5 (45.45%) among the study subjects in Group B with serum IGF-I <175.9ng/ml. p-value was 0.003 which was significant.

Figure 1 shows ROC curves of serum IGF-I in predicting preeclampsia. Result shows that area under curve was 0.801, lower bound was 0.614 and upper bound 0.988. P value was 0.011 at 95% CI.ROC Curve shows around 80% sensitivity and 20% false negative rate (FNR). Table 3 shows AUC of serum IGF-I in prediction of preeclampsia. Area under curve (AUC) of serum IGF-I was 0.801 in prediction of preeclampsia. P-value was 0.011 which was significant.

Table 4 shows sensitivity, specificity, PPV and NPV of serum IGF-I in prediction of preeclampsia. Sensitivity, specificity, PPV, NPV and accuracy of serum IGF-I (at cut off value 175.9 ng/ml) was 71.4%, 87.0%, 45.5%, 95.2% and 84.9% respectively. Figure II shows that among the patients with preeclampsia, Serum IGF-I level was 167.48 ng/ml and in normal pregnancy it was 251.8 ng/ml . P value was .011 which was significant.

Table 1: Demographic profile of the patients (n=53)

Variables	**Normal IGF-I, Group A, n = 42**	**Low IGF-I, Group B, n= 11**	**p-value**
Age (mean ± SD)	26.28± 6.07	24.28± 6.57	0.441
Gravida			
Primi	25 (59.52%)	7 (63.63%)	1.000
Multi	17 (40.47%)	4 (36.36%)	

Table 2: Association of development of Preeclampsia with serum IGF-I at cut off value 175.9 ng/ml (n=53)

Serum IGF-I (ng/ml)	**Preeclampsia**	**Normal Pregnancy**	**Total**	**p-value**
Group A normal level of IGF-I (>175.9) n=42	2 (4.76%)	40 (95.23%)	42 (79.2%)	0.003
Group B low level of IGF-I (<175.9) n= 11	5 (45.45%)	6 (54.54 %)	11 (20.75%)	
Total	**7**	**46**	**53**	

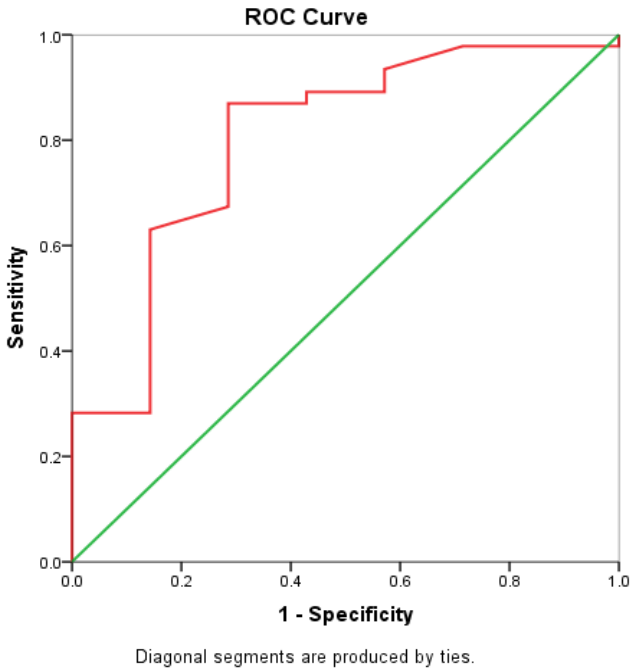

Figure 1: ROC curve of serum IGF1 in prediction of preeclampsia (n=53)

Table 3: AUC of serum IGF-I in prediction of preeclampsia (n=53)

Variable	Area	SE	p-value	95% CI	
				Lower Bound	Upper Bound
Serum IGF1	0.801	0.095	0.011	0.614	0.988

Table 4: Validity of serum IGF-I in prediction of preeclampsia (n=53)

Serum IGF-I(ng/ml) (Cut off value)	Sensitivity	Specificity	PPV	NPV	Accuracy
175.9	71.4	87.0	45.5	95.2	84.9

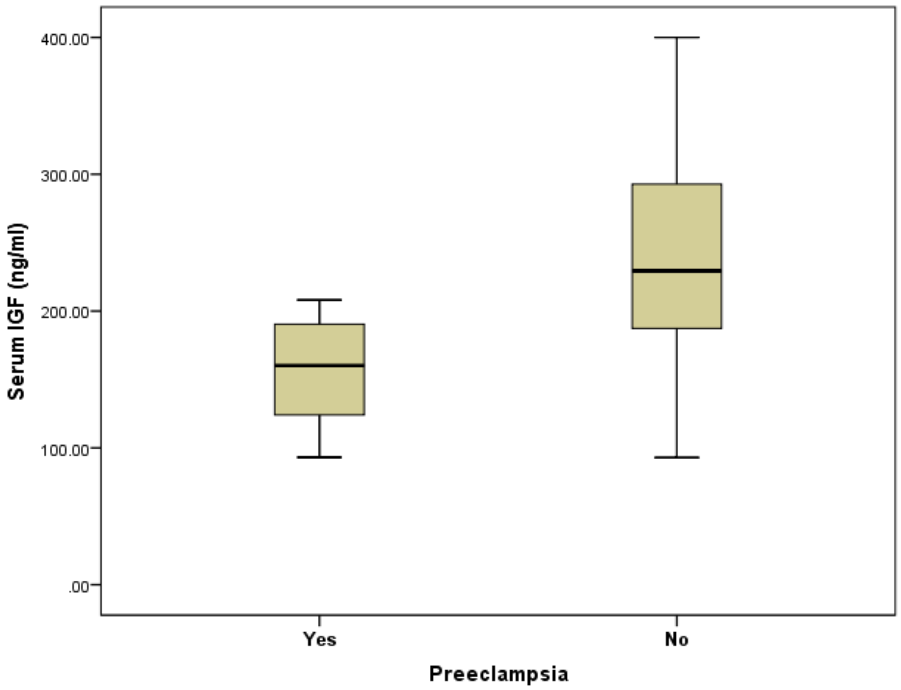

Figure 2: Box plot of serum IGF-I in preeclampsia patients and normal pregnancy (n=53)

DISCUSSION

Preeclampsia is one of the most common pregnancy complications. Preeclampsia is associated with significant morbidity and mortality for mother and fetus. Insulin-like growth factors are important regulators of cell proliferation and differentiation and apoptosis. Circulating IGF-I is primarily derived from the liver. IGF-I remain stable until 20 weeks and then increase whereas IGF-II values do not relatively change throughout gestation. So IGF-I was measured in this study. Low IGF-I from the first to second trimester was associated with higher risk of preeclampsia.

In this study, total 53 patients were included. The mean ± SD age of the patients with normal IGF-I (Group A) was 26.28± 6.07 years and patients with low IGF-I (Group B) was 24.28 ± 6.57 years. The maternal serum IGF-I concentration in normal pregnancy increased with gestational age. ROC curve of serum IGF-I showed that area under curve (AUC) of serum IGF-I was 0.801 (lower bound 0.614 and upper bound 0.988) in prediction of preeclampsia (p value was 0.011 with 95% confidence interval). According to Youden index the best cut off value of serum IGF-I was 175.9 ng/ml in prediction of preeclampsia.

Present study revealed that, 7 patients developed preeclampsia among them 5 patients (45.45%) was in Group-B (low IGF-I <175.9 ng/ml) and 2 patients (4.76%) was in Group-A (normal IGF-I >175.9 ng/ml) in Chi-square value. This association showed preeclampsia was significantly higher among study subjects in Group-B (serum IGF-I <175.9 ng/ml) with P- value 0.003. Present study found that, the sensitivity of serum IGF-I (at cut off value 175.9 ng/ml) was 71.4% and specificity of serum IGF-I (at cut off value 175.9 ng/ml) was 87.0% and positive predictive value (PPV) of serum IGF-I (at cut of value 175.9 ng/ml) was 47.5% and negative predictive value was 95.2%. Accuracy of serum IGF-I (at cut off value 175.9 ng/ml) was 84.9%.

According to a recent study, the maternal serum levels of IGFI remain stable until 20 weeks and then increase whereas IGF-II values do not relatively change throughout gestation. An increase in IGF-I from the first to second trimester was associated with higher risk of preterm preeclampsia. Low concentrations of IGFBP-1, both in the first and in the second trimesters, were related to higher risk of term preeclampsia and moderately increased risk of preterm preeclampsia [9]. E.A Dubova *et al.,* 2014, studies comparative morphhological study of the placentas in women with preeclampsia assessed expression of IGF-I by immunohistochemical methods showed, low expression of IGF-I in the placental tissue depending on preeclampsia severity were detected [17].

In the previous study, the findings showed a significant reduction of IGF-1 in preeclamptic placentas and hypoxic trophoblasts, and a remarkable hypermethylation of IGF-1 promoter region in preeclamptic placentas [12]. Early identification of women who are at high risk for development of preeclampsia could potentially improve pregnancy outcome because intensive maternal and fetal monitoring in such patients would lead to an earlier diagnosis of the clinical signs of the disease and the complications related to preeclampsia. Development of serious complications can be avoided for these patients through interventions like administration of antihypertensive medication and early delivery. Therefore IGF-I can be a useful test for early detection of preeclampsia.

CONCLUSION

Present study concluded that values of IGF-I were found low in preeclampsia patients than normal pregnancy. Association between development of preeclampsia and concentration of IGF-I was significant. Relative risk of development of preeclampsia increases when concentration of IGF-I was lower than normal in early pregnancy (8 to 15 weeks). So measurement of IGF-I can help Obstetrician by raising awareness about the development of preeclampsia and subsequent adverse conditions.

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