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Association of serum soluble endoglin with preeclampsia

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***Abstract*---**Objectives: To determine and compare the serum soluble Endoglin (sEng) levels among pregnant women with preeclampsia (PE) and women having normal pregnancy. Methodology: This cross-sectional study was carried at IBMS KMU and the data collection was carried out in the department of Gynecology & obstetrics, Lady Reading hospital, Peshawar, from June 2019 to July 2020. A total of 138 pregnant women at the gestational age of 26-30 weeks were included. The study sample was divided into two groups. Group A: Pre-Eclamptic (n=92). Group B: Normotensive Control Group; women with normal pregnancy (n=46). Results: Mean age in PE group was considerably lower as compared to control group ($p<0.001$). Similarly, mean age at the time of marriage was significantly lower in the PE group compared to control group (19.40±1.92 vs 21.17±2.19 years, $p<0.001$). Both mean systolic and diastolic blood pressure in PE and

control group was noted to be significantly differed (169.78 ± 16.64/ 114.62 ± 9.34 vs 119.57 ± 1.07/ 78.48 ± 5.56 mm Hg, p<0.05). PE group had statistically significantly higher sEng levels compared to control group (13.42 ± 2.94vs3.47 ± 2.80 ng /ml, p <0.001). Conclusion: Maternal sEng levels were notably elevated in women with PE than normotensive pregnant women. sEng has the potential for use as predictive clinical test for preeclampsia and could possibly improve the pregnancy outcome.

Keywords---Serum soluble endoglin levels, pregnancy, preeclampsia, Blood pressure.

Introduction

Preeclampsia (PE) is a multifactorial pregnancy related disorder which can be caused by different factors such as immunologic, hematologic, genetic and environmental ones[1] and remains a major determinant of maternal and fetal mortality and morbidity morbidity.[2] PE is characterized by hypertension of greater than 140 and 90 mm Hg and proteinuria of greater than 300mg per 24 hours after 20th week of gestation.[3] The most effective treatment till now is the early delivery of placenta suggestive of the fact that it is the main culprit in this diseases. [4]

A disproportion among the angiogenic and anti-angiogenic factors are involved in the pathophysiology of preeclampsia.[1,5] It is believed that the inadequate placentation is involved in the increased levels of these anti-angiogenic substances.[6] Placental ischemia is considered to induce the preeclampsia that results in fetal distress and dysfunction which result in the release of soluble factors into the maternal blood stream and causing the symptoms related with preeclampsia.[7,8] Several studies suggested that the placental ischemia and hypoxia may cause the increased expression of antiangiogenic serum soluble endoglin.[9]

Soluble endoglin play a major role in the pathophysiology of preeclampsia. Soluble endoglin are cleaved from the placental surface in patients with preeclampsia and released into the maternal blood stream, causing endothelial cell dysfunction and eventually hypertension.[10,11] In the past few years it is proposed that the potential roles of soluble endoglin are involved in the preeclampsia.[12] Soluble endoglin serve as co-receptor for transforming growth factor of beta family. It is mainly expressed on the cell membrane of vascular endothelium and syncytiotrophoblast which is the outermost layer of placenta immersed into the blood.[13]

The aim of the study is to evaluate the levels of serum soluble endoglin in women with preeclampsia and compare it with normotensive pregnant women to better understand its role in preeclampsia.

Methodology

This cross-sectional study was carried at IBMS KMU and the data collection was carried out in the department of Gynecology & obstetrics, Lady Reading hospital, Peshawar, from June 2019 to July 2020. A total of 138 pregnant women at the gestational age of 26-30 weeks were registered in the study. Women with prior history of diabetes, renal diseases, hypertension, twin pregnancies etc. were excluded from the study. The study sample was divided into two groups. Group A: Pre-Eclamptic (n=92). Group B: Normotensive Control Group; women with normal pregnancy (n=46). Participant's demographic and clinical information including age at marriage, education, husband education, occupation, monthly income, history of pregnancy, gestational age, sign and symptoms of preeclampsia, complications and hypertension were recorded.

Blood sample (5ml) was taken from the study participants through custom method applying aseptic techniques. The samples in both groups were isolated with proper tagging. Three ml of blood was transferred to a gel tube. Each blood sample was instantly centrifuged at 1000 rounds per minute to get a clear serum and stored at -20 centigrade in a freezer at IBMS (Institute of Basic Medical Sciences) Khyber Medical University, Peshawar. While determination of sEng was carried out by commercially available Elisa kits in IBMS.

Sample Preparation for sEng levels were done as "Fresh whole blood sample collected in K3-EDTA anticoagulated vacutainer was used preceding to sampling. The sample was softly mixed by inverting it 11 times to accomplish a homogenous sample. Shaking the tube could destroy the blood cells and was taken off and the aspiration needle was engrossed well into the sample. The sampling bar was pressed to start measuring full blood count. During aspiration, the sampling tube held in a constant position. The instrument illustrates 25µl of sample, and the aspirating needle is retracted while its outer surface is automatically rinsed with diluents. When the status LED started blinking and the beeps heard signifying the end of the sampling process. The sampling tubes was removed and recapped. An external PC keyboard was coupled with the instrument to acquire the results. At the end of a measuring process, all measured and calculated parameters were displayed on the screen and a printout was taken".

Both systolic and diastolic blood pressure was measured with typical mercury sphygmomanometer and typical arm cuff at the right arm. Participants were either in sitting position and the calculations was taken after intervals of 5 minutes relax in the pose of recording. The recordings were taken at interval of 5 minutes each and their average values were noted. Computer software package SPSS Version 26 was used for data analysis. Frequency and proportions were calculated for categorical data, while mean and standard deviation was calculated for numerical data. Mean differences were computed using student's t test and association was determined using chi square test. A p-value of less than 0.05 ($p<0.05$) was considered to be significant.

Results

A total of 138 women (preeclamptic n=92 and normal pregnancy as a control n=46) with ages ranging from 17-26 years were approached for data collection. Sociodemographic, obstetric history and family history of hypertension of both groups are summarized in **Table 1.** Mean age of patients in preeclamptic group was lower (20.83±1.96 years) as compared to control group (22.93±2.11 years) and the differences were statistically significant (p<0.001). Of the total 138, 86 (62.3%) of the patients had no formal education and majority 73(79.35) were from preeclamptic group. Education level was significantly differed across the study group. Majority, 131(94.9%) of the women were house wives, government and private jobs were occupied by 4.3% and one woman having private job. Nearly 43% of the patients had monthly income of 2500-5000 Pakistani rupees. The association of monthly income was significant between the two groups. Age at the time of marriage of (19.40±1.92 years) was significantly lower in the preeclamptic group, compared to control group (21.17±2.19). Regarding parity, majority were primiparous. Family history of hypertension of was reported by 47.83% preeclamptic group and the difference was significant between the groups. Moreover, no significant difference between the two groups in terms of family history of pregnancy induced hypertension was found.

Anthropometric and Blood Pressure (BP) of the study participants are depicted in Table 2. Both groups were compared based on the anthropometric parameters, significant mean differences in weight, height between the study groups was observed. Mean weight of pregnant in preeclamptic group were higher as to normo-tensive group. Furthermore, both systolic and diastolic blood pressure was significantly higher in preeclamptic group than control group (p<0.001). The endoglin levels were determined in both study groups. Statistically significant endoglin mean difference was observed between pre-eclamptic group (13.42 ± 2.94 ng /ml) and control group (3.47 ± 2.80 ng /ml) p <0.001 and can be seen in Figure 1.

Table 1. Socio-demographic, obstetric history of study population

Characteristics		Total	PE Group N=92	Control Group N=46	p Value
Age (years) Mean±SD		21.53±2.24	20.83±1.96	22.93±2.11	<0.001
Education Levels	No formal education	86 (62.3)	73 (79.35)	13 (28.26)	<0.001
	Primary level	7 (5.1)	7 (7.61)	0 (0)	
	Secondary	17 (12.3)	9 (9.78)	8 (17.39)	
	Higher Secondary	6 (4.3)	1 (1.09)	5 (10.87)	
	University level	22 (15.9)	2 (2.17)	20 (43.48)	
Occupation	Government Servant	6 (4.3)	1 (1.09)	5 (10.87)	0.010
	House Wife	131 (94.9)	91 (98.91)	40 (86.96)	
	Private Servant	1 (.7)	0 (0)	1 (2.17)	
Monthly income (PKR)	2500-5000	59 (42.8)	59 (64.13)	0 (0)	<0.001

	5001-10000	32 (23.2)	24 (26.09)	8 (17.39)	
	>10001	47 (34.1)	9 (9.78)	38 (82.61)	
Age at marriage (years)		19.99±2.18	19.40±1.92	21.17±2.19	<0.001
Gravidity (N=136)	1st	145 (97.8)	90 (100)	45 (97.83)	0.338
	2nd	1 (0.7)	0 (0)	1 (2.17)	
Family Hx of HTN	No	94 (68.1)	48 (52.17)	46 (100)	<0.001
	Yes	44 (31.9)	44 (47.83)	0 (0)	
Family Hx of Pregnancy induced HTN	No	133 (94.4)	87 (94.57)	46 (100)	0.169
	Yes	5 (3.6)	5 (5.43)	0 (0)	

Table 2. Anthropometric & BP of the study participants

Characteristics	Total	PE Group N=92	Control Group N=46	p Value
Weight (kg)	70.75±7.44	73.40± 7.37	65.46±3.99	<0.001
Height (m)	150.97±11.59	146.69±10.39	159.54±8.85	<0.001
Systolic BP	153.19±27.70	170.00±16.69	119.57±6.22	<0.001
Diastolic BP	102.68±19.09	114.78±9.43	78.48±5.56	<0.001

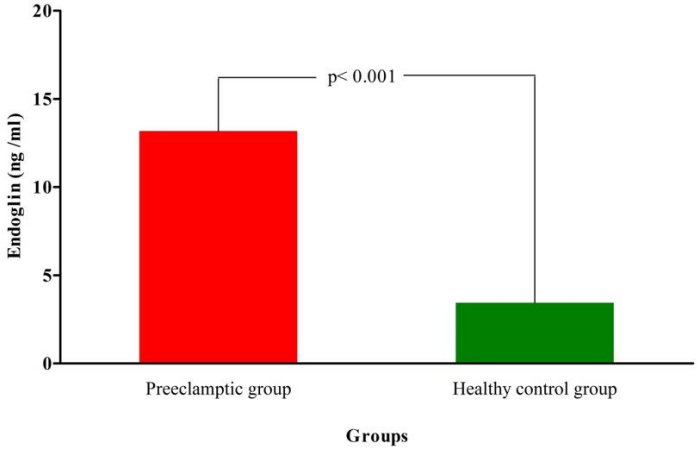

Figure 1: Mean comparison of serum sEng in PE Group vs Control Group

Discussion

PE is more common in women's of young age.[14] Our results showed that mean age of patients in PE group was lower as compared to normo-tensive pregnant women. Nearly half of the of patients were reported in the age of <20 years in PE group, which depicts that PE is common in younger age pregnant women.The vulnerability of PE is privileged when the age of pregnant subjects is not as much of 25 years of age. [15] A study from India illustrates that patients with first pregnancy linked with PE of < 20 years of age were 26% while only 15% of controls were < 20 years [16] indicative of that the younger age of pregnant women

is one of the attribute that leads to PE. Consequently it can be implicit from the outcome of our research study that younger mother age had a major manipulate in causing PE. In this study pre-eclamptic group (79.3%) women were those who got married at the age of 16 to 20 years while in controls group (78.26%) of women were those who got married at the age of above 20 years. Hence it can be accomplished from our study that the women who get married at <20 years or adolescent are more exposed to develop preeclampsia. Even though no such records are offered in literature to contemplate on this factor.

Mean systolic and diastolic blood pressure in PE and control group was noted to be significantly differed (169.78 ± 16.64/ 114.62 ± 9.34 **vs** 119.57 ± 1.07/ 78.48 ± 5.56 mm Hg, $p<0.05$). The results of our study can also be supported by the other study done in Korea.[17] where the mean systolic and diastolic blood in pre-eclamptic women were (155.1±15.6/97.4±13.9) mm Hg, were compared with control group in which mean systolic and diastolic blood pressure were (119.3±9.2/ 75.8±7.6) mm Hg.

Our study results correlate well with the results of other studies. In findings of our study the women in pre-eclamptic group had elevated levels of sEng (13.42±2.94 ng/ml) as compared to women in normo-tensive group (3.47±2.80ng/ml). Other studies also show a noteworthy increase in sEng levels in pre-eclamptic group as compared to normo-tensive pregnant group. In our study (56.5%) women of pre-eclamptic group had sEng levels greater >14ng/ml, (29.34%) women had values between 14 -9.1 ng/ml as compared to normo-tensive group in which (78.2%) of women had endoglin in the normal range of 0-4 ng/ml. The results of our findings are consistent with other previous studies which also show the elevation of soluble endoglin levels in preeclampsia.[18]

Placental ischemia causes the freeing of placental factors and a disproportion of angiogenic factors, consequently leads to endothelial dysfunction in preeclampsia and distorted appearance of antiangiogenic peptides (like soluble endoglin) from it. A study by Rekha Sachan et al 2016 was carried out to assess the diagnostic value of sEng preeclampsia. They observed increased levels of sEng in the preeclamptic group.[19] In another study by Pooneh Nikeuei et al 2017 showed a significant increase in levels of sEng in preeclamptic women as compared to normal pregnant women.[20] Moreover, a study by Georgia Marigioula-Siarkou et al 2021., on the diagnostic role of sEng in different trimesters of pregnancy. Their results showed the increase levels in 2nd and 3rd trimesters of pregnancy.[21] Lamyaa Taha Muhammed et al 2021., described the role of soluble endoglin in the diagnosis of preeclampsia severity in Iraqi women showed high levels of sEng in preeclamptic groups as compared to normotensive pregnant women. [22]

Conclusion

Maternal sEng levels were notably elevated in women with PE than normotensive pregnant women. These outcomes designate the prognostic value of sEng as a laboratory indicator of preeclampsia. Further studies on higher number of women and other ethnic group is required to re-evaluate the significance of this marker, moreover other antiangiogenic markers may be needed to be evaluated and correlated with other for accurate and earlier prediction of preeclampsia. Since

the serum concentrations of these bio markers rise just about 6 weeks prior to the commencement of the symptoms, enlarged serum levels of these factors on the situation of labile blood pressure or ambiguous presence of protein in urine may recognize patients who would grow the complete symptoms and signs of preeclampsia soon after. Possible investigative, proper observation and punctual medical involvement would be helpful in women with preeclampsia.

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