PLASMA FIBRIN DEGRADATION PRODUCTS (FDP) IN PATIENTS WITH PRE ECLAMPTIC TOXAEMIA (PRE-ECLAMPSIA)

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Summary

Plasma fibrin degradation products (F.D.P.) assay measures the amount of fibrin split products in the blood. The high levels of F.D.P. in pre-eclampsia suggests that abnormal amount of degradation products are most likely due to localized lysis of fibrin in the uterine vascular compartment. The present case control study was designed to determine the relationship between plasma fibrin degradation products and pre-eclampsia. The study was carried out in the department of Biochemistry, Chittagong Medical College during the period of September 2011 to August 2012. The samples were collected from the department of Obstetrics and Gynecology, Chittagong Medical College Hospital, age from 18- 40 years. The data were collected by a structured questionnaire including age, socioeconomic condition, gravida, para, edema, blood pressure, proteinuria, history of hypertension, family history of pre-eclampsia and diabetes mellitus. Considering the cost of experiment and length of time, total 60 patients were included in this study. Among them 40 were considered as case (Blood Pressure > or = 140/90 mm of Hg and proteinuria > 0.3 gram/day) and 20 were considered as control (Blood Pressure < 140/90 mm of Hg and no proteinuria). Plasma fibrin degradation products were measured in all samples. Study showed that plasma FDP were more increased in pre-eclamptic patients than that of normal pregnancy (21.52 + 16.47 µgm/ml Vs 10.63 + 7.12 µgm/ml), P = <0.01. Result showed that percentage of raised plasma FDP is more in pre-eclamptic patients (100%) than that of normal pregnancy (75%), P= <0.01. Pearson's Correlation Coefficient (r) showed that there were positive correlation between blood pressure and plasma FDP (systolic blood plessure and plasma FDP, r=0.221,P=>.0.05 and diastolic blood pressure and plasma FDP, r=0.285,P=<0.05). Significantly* **raised** *level of plasma F.D.P. in pre-eclampsia help to formulate a management plan and thereby reduce the complications of this disease.

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Key words
Pre-eclampsia; fibrin degradation products; hypertension; proteinuria

Introduction

Pre-eclampsia occurs in about 6% of the general population[1]. The incidence varies with geographic location. Predisposing factors are nulliparity, black race, maternal age below 20 or above 35years, low socioeconomic status, multiple gestation, hydatidiform mole, polyhydramnios, nonimmune fetal hydrops, twins, obesity, diabetes, chronic hypertension, and underlying renal disease [1]. Exact cause of pre-eclampsia is not known. Although some researchers suspect poor nutrition, high body fat or insufficient blood flows to the uterus are possible causes [2]. In contrast with advances made in treating or eliminating many other serious disorders, severe morbidity and mortality associated with pre-eclampsia/eclampsia remain among the leading problems that threaten safe motherhood particularly in developing countries [2].

Overall level of F.D.P. are significantly increased in pre-eclampsia, and strikingly increased in eclampsia. F.D.P. level are higher in the third trimester of normal pregnancy than in the first two trimesters. In pre-eclampsia F.D.P. are significantly higher in both before the onset of labour and postpartum than in the comparable stages of normal pregnancy [3]. The F.D.P assay measures amount of the fibrin and fibrinogen split products in the blood and directly indicate the level of activity of the fibrinolytic system. High levels of FDP will indicate increased fibrinolysis . Primary fibrinogenolysis is a condition in which fibrinogen is broken down to fibrin in the absence of a clot. Unlike DIC, the formation of intravascular thrombi does not occur. However, if severe, hemorrhage can result because the body's supply of fibrinogen becomes depleted. Causes include shock, hypoxia, heat stroke, hemorrhage, surgery, and liver disease [4]. Raised F.D.P. in pre-eclampsia and eclampsia are due to secondary fibrinogenolysis and that mainly fibrin degradation products are being measured [3].

Pregnancy normally induces appreciable increases in the concentrations of coagulation factors I (fibrinogen), VII, VIII, IX and X. The haemostatic mechanism would appear to be altered towards a physiological hypercoagulability with an enhanced

capacity to form fibrin and a diminution in the ability to lyse fibrin. In the presence of diminished fibrinolytic activity in the circulation, the increased level of F.D.P. may be explained by the lysis of fibrin in localized areas of the vascular system. F.D.P. level may reflects fibrinolysis occurring in vivo in response to intravascular fibrin deposition [5].

The uterus is a potent source of plasminogen activator and uterine action during labour is accompanied by transient myometrial ischemia. Circumstances therefore may exist for the local release of activator, and this may then be absorbed on placental fibrin with consequent local fibrinolytic activity in the placental circulation. An enhanced fibrinolytic activity in the uterine circulation during labour could be a natural defense mechanism to maintain the maternal blood supply to the placenta by ensuing patency of the placental bed during labour. The high level of F.D.P. in pre-eclampsia/eclampsia in association with greatly diminished lytic activity in the circulation suggests that the abnormal amount of degradation products are most likely the result of localized lysis of fibrin in the vascular compartment. The raised F.D.P. level indicates that in these complications both intravascular fibrin formation and fibrin proteolysis are taking place [5].

Pre-eclampsia is a syndrome characterized by the onset of hypertension (>or =140/90 mm of Hg) with proteinuria (>0.3 gram/day or >300mgm/day) in a previously normotensive and non-proteinuric woman after 20 weeks of gestation. Some amount of edema is common in normal pregnancy. Edema has been excluded from the diagnostic criteria unless it is pathological. Demonstration of pitting edema over the ankles after 12hours bed rest or rapid gain in weight of more than 1 lb a week or more than 5 lb a month in the last months of pregnancy may be the earliest evidence of pre-eclampsia. Presence of total protein in 24 hours urine of more than 0.3 gram or 300mgm in the absence of urinary tract infection is considered significant [6].

A more basic abnormality of pre-eclampsia is usually generalized arteriolar constriction and increased vascular sensitivity to pressor peptides and amines. An early abnormality noted in women who develop pre-eclampsia is the failure of the second wave of trophoblastic invasion into the spiral arteries of the uterus. As a result, there is failure of the cardiovascular adaptation to normal pregnancy, resulting in reduced cardiac output and plasma volume. These abnormalities also result in impaired tissue perfusion [7].

Abnormal activation of the clotting system is an early and occasionally the first detectable feature of pre-eclampsia [8]. Pre-eclampsia rates vary from 5% to 10% of nulliparous women, to much higher rates in women with medical comorbidities or fetal factors (e.g. multiple gestations, molar pregnancies, hydrops or triploidy). Pre-eclampsia's pathogenesis is attributed to abnormal placental implantation with abnormal maternal immune adaptation, altered maternal angiogenic factors with increased systemic vascular resistance and endothelial dysfunction leading to the clinically apparent maternal syndrome [9].

Abnormal intracellular calcium metabolism in platelet and red cell has been demonstrated in women with pre-eclampsia. Women considered to be at high risk for developing pre-eclampsia have suggested a reduction in the incidence of the disease among women receiving supplemental calcium [10].

The characteristic lesion of pre-eclampsia, glomeruloendotheliosis is a swelling of the glomerular capillary endothelium that causes decreased glomerular perfusion and glomerular filtration rate [11].

Eclampsia is one of the grave diseases, which still contributes 20% of the maternal mortality in Bangladesh [12]. This incidence of maternal mortality from such a serious complication can only be reduced by antenatal care, early diagnosis of pre-eclampsia, adequate medical management and judicious medical and obstetric interference [13]. Increased F.D.P. in pre-eclampsia help to formulate a treatment plan to combat complications of this disease.

Materials and methods

The case-control study was carried out in the department of Biochemistry and department of Gynecology and obstetrics, Chittagong Medical College Hospital from September 2011-August 2012. Proper permission was taken from the Ethical Committee of Chittagong Medical College. Total 60 subjects of age between 18 – 40 were included in this study. Among them 40 were case (Group A) (pre-eclamptic patients) whose blood pressure was =or > than 140/90 mm of Hg and proteinuria > 0.3 gm/day (after 20 weeks of gestation) and 20 were control (Group B) (third trimester of normal pregnancy) whose blood pressure was <140/90 mm of Hg and no proteinuria. Patients suffering from diseases which causes raised fibrin degradation products level such as deep venous thrombosis, sickle cell anemia , leukemia, and history of taking drugs like barbiturate, heparin, streptokinase, urokinase and habit of smoking were excluded from the study group.

Estimation of plasma F.D.P. :-
F.D.P level was estimated by Latex Immunoassay method in Automated Blood Coagulation Analyzer, CA-550.
Normal level of plasma fibrin degradation products (F.D.P.) are < 5.0 microgram/ ml [14]. Above which marked as raised level.

Data analysis
Data were analyzed by computer based software SPSS v-18. Data were expressed as mean + SD. Confidence level was fixed at 95% level and "p" value of 0.05 or less was considered significant. Student's 't' test for quantitative or continuous variable and Chi-square test for categorical variable were done.

Results

Total 60 subjects were included in this study. Of them 40 were in Group A (case group) and 20 were in Group B (control group). Majority of the participants (66.7%) live in the rural areas and rests (33.3%) in the urban areas. 61.7% of the participants are from poor socioeconomic status followed by average socio-economic status (38.3%). Most of the participants (83.3%) are illiterate and rests (16.7%) are literate. Results are shown in Table-I.

Mean systolic blood pressure and diastolic blood pressure are highly increased in Group A than that of Group B, which is statistically highly significant ($p < 0.001$; t test). Result is shown in Table-II.

Plasma FDP are more increased in Group A than that of Group B, which is statistically highly significant ($p < 0.01$; t test). Result is shown in Table – III.

Percentage of raised plasma FDP is more in Group A than that of Group B, which is statistically highly significant ($p < 0.01$; t test). Result is shown is Table-IV.

There are positive correlation coefficients among systolic blood pressure and diastolic blood pressure with plasma FDP, and is statistically significant for diastolic blood pressure ($p < 0.05$). Result is shown is Table-V.

Table I : Distribution of socio-demographic variables among the study groups

Socio-Demographic Variables		Study Groups				Total	
		Group A		Group B			
		N	%	N	%	N	%
Inhabitance	Rural	32	80.0	08	40.0	40	66.7
	Urban	08	20.0	12	60.0	20	33.3
	Total	40	100.0	20	100.0	60	100.0
Socio-Economic	Poor	28	70.0	09	45.0	37	61.7
Status	Average	12	30.0	11	55.0	23	38.3
	Total	40	100.0	20	100.0	60	100.0
Educational	Illiterate	38	95.0	12	60.0	50	83.3
Status	Literate	02	5.0	08	40.0	10	16.7
	Total	40	100.0	20	100.0	60	100.0

Table II : Distribution of blood pressure among the study groups (with t-test significance)

		N	Mean	± SD	Median	Range	Significance
Systolic BP	Group A	40	161.50	16.10	160.00	130 – 200	*P < 0.001
(mmHg)	Group B	20	106.00	11.88	100.00	90 – 130	
	TOTAL	60	143.00	30.21	150.00	90 – 200	
Diastolic BP	Group A	40	110.88	9.99	110.00	90 – 130	*P < 0.001
(mmHg)	Group B	20	76.25	7.76	80.00	60 – 85	
	TOTAL	60	99.33	18.88	105.00	60 – 130	

*Highly significant

Table **III :** Distribution of plasma fibrin degradation products among the study groups (with **t** – test significance)

		N	Mean	± SD	Median	Range	Significance
Plasma	Group **A**	40	21.52	16.47	15.60	12.10 – 81.70	
FDP							*P < 0.01
(µg/ml)	Group **B**	20	10.63	7.12	7.45	2.40 – 22.10	
	TOTAL	60	17.89	14.91	15.15	2.40 – 81.70	

*Highly significant

Table **IV :** Percentage distribution of plasma fibrin degradation products among the study groups (with X^2 test significance)

		Study Groups				Total		Significance
		Group A		Group B				
		n	%	n	%	n	%	
Plasma FDP Status	Normal (< 5 µg/ml)	00	0.0	05	25.0	05	8.3	*P < 0.01
	Elevated	40	100.0	15	75.0	55	91.7	
	Total	40	100.0	20	100.0	60	100.0	

**Highly significant

Table **V :** Correlation between blood pressure & plasma fibrin degradation products

Correlation between	Pearson's Correlation Coefficient (r)	Significance (P Value)
Systolic Blood Pressure & Plasma FDP	0.221	P > 0.05
Diastolic Blood Pressure & Plasma FDP	0.285	P < 0.05

Discussion
The aim of this study was designed to observe the relationship of plasma fibrin degradation products with pre-eclampsia (pre-eclamptic toxemia).
The present study provides the data on the relationship of plasma fibrin degradation products with pre-eclampsia and normal pregnancy.

Pre-eclampsia occurs in about 6% of the general population. The incidence varies with geographic location [1]. In contrast with advances made in treating or eliminating many other serious diseases, severe morbidity and mortality associated with pre-eclampsia/eclampsia remain among the leading problems that threaten safe mother-hood particularly in developing countries [2].

Among the study groups 6.7% were below 20 years, 85.0% were 20 to 30 years and 8.3% were above 30 years. In the study population 66.7% live in the rural areas, 33.3% live in the urban areas. 61.7% of the participants are from poor socio-economic status and 38.3% are from average socio-economic status. 83.3% of the participants are illiterate and 16.7% are literate.

The study population was divided into two groups, group A and group B designed as case and control in the existing methodology. The case was defined as those having hypertension (Blood Pressure > or = 140/90 mm of Hg) and proteinuria >0.3 gram/day and the control having no hypertension (Blood Pressure < 140/90 mm of Hg) and no proteinuria. In both case and control known case of deep venous thrombosis, sickle cell anaemia, leukemia, diabetes mellitus were excluded because these diseases may increase blood fibrin degradation products level. The person with a history of taking drugs like barbiturate, heparin, streptokinase, urokinase and habit of smoking were also excluded.

In this study average ages of the cases were 25.42 ± 4.61 years and the controls were 23.95 ± 5.69 years. The average systolic blood pressure of the cases were 161.50 ± 16.10 mm of Hg and diastolic blood pressure were 110.88 ± 9.99 mm of Hg and average systolic blood pressure of the controls were 106.0 ± 11.88 mm of Hg and diastolic blood pressure were 76.25 ± 7.76 mm of Hg.

In present study it is observed that plasma fibrin degradation products in pre-eclamptic patients are more than that of normal pregnancy (21.52 ± 16.47 µgm/ml Vs 10.63 ± 7.12 µgm/ml) which is statistically highly significant. Similar kind of observations are also read in other studies [3,5,15,17]. But in another study found no difference of fibrin degradation products between the group with pre-eclampsia and normal pregnant patients [18].

In the results of this study, percentage distribution of plasma FDP between the group of pre-eclamptic and normal pregnant patients were found to be statistically highly significant (P=< 0.01). Percentage of raised plasma fibrin degradation products were more in pre-eclamptic patients(100%)than that of normal pregnancy (75%). The findings are more or less similar to that of other studies [3,5,15-17].

In present study, Pearson's Correlation Coefficient(r) showed that there was a positive correlation between systolic blood pressure and plasma fibrin degradation products (r= 0.221, P= >0.05), Diastolic blood pressure and plasma fibrin degradation products (r= 0.285, P=<0.05) . This may be due to inclusion of such cases which are more severe in form or otherwise compensatory response to the presence of fibrin deposition in the vascular compartment [17]. Fibrin deposition in the renal vasculature could result in glomerular damage and proteinuria. Hypertension may be the result of renal ischemic change or a compensatory response to the presence of fibrin deposition in the vascular compartment [17].

Intravascular clotting is taking place in pre-eclampsia and this disturbance of the balance between coagulation and fibrinolysis may be localized to certain areas of the vascular compartment, particularly the placenta and renal circulation. Fibrin deposition in the maternal vessels supplying the placenta would impair the placental blood flow, which may explain the placental insufficiency which occurs in pre-eclampsia. Likewise fibrin deposition in the renal vasculature will result in glomerular damage and proteinuria. Hypertension may be related to the renal ischemic change or a compensatory response to the presence of fibrin deposition in the vascular compartment [17].

The presence of fibrin degradation products in the plasma of pregnant nonpreeclamptic women may be due to the overall increased metabolic state of pregnancy [15].

Limitations of the study

Small sample size.

Conclusion

The proportion of maternal mortality rate from the complications of pre-eclampsia is large enough to demand special attention and action. In the primary care setting there is a strong need to increase public awareness about identification and prevention of pre-eclampsia which will help in reducing the maternal mortality rate due to the complications of pre-eclampsia.

Therefore patient awareness and education is the cornerstone of disease prevention. Since pre-eclampsia is accompanied by low socioeconomic condition, obesity, hypertension that increases the risk of complications of pre-eclampsia such as eclampsia, pre-eclampsia is to be considered one of the major health issues. Government should take measures to improve public awareness about safe pregnancy, safe delivery and better socioeconomic condition. Early detection and prevention of pre-eclampsia can help to reduce morbidity and mortality to a greater extends in this regard.

Disclosure

All the authors declared no competing interest.

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