RESEARCH PAPER | Medical Science | Volume : 5 | Issue : 10 | October 2015 | ISSN - 2249-555X

Correlation between Fibrinogen and Mean Arterial Pressure Levels in Pre-eclamptic Women

KEYWORDS: Fibrinogen; Mean Arterial Pressure; Pre-eclampsia

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ABSTRACT *Fibrinogen, a major heterogenous coagulation plasma protein, is involved in the hypercoagulability and the angiogenic imbalance seen in early onset of pre-eclampsia. Blood pressure is an indicator for the severity of pre-eclampsia. In this study 100 patients with pre-eclampsia were studied out of which 50 were mild and 50 were severe pre-eclamptics. They were compared with 50 healthy subjects. Subjects were of similar gestational age, body mass index (BMI) and parity matched. They were all primigravidas at third trimester of pregnancy. All studied subjects belonged to age group 28-40 years. A significant strong positive correlation was seen between fibrinogen and mean arterial pressure levels (r=0.2) in mild, severe pre-eclamptics (r=0.15) and among healthy control group (r=0.05). So it is felt that it may be useful in prediction and diagnosis of the severity of pre-eclampsia.*

Introduction –

Pre-eclampsia is a complication of pregnancy constituting a major cause of maternal morbidity and mortality worldwide. The cardinal clinical features of the condition are hypertension, edema and proteinuria occurring after 20 weeks of gestation in women who were not previously known to be hypertensive[1]. Hypertension was defined as 140 mmHg systolic and 90 mmHg diastolic blood pressure, when measured on 2 consecutive occasions at least 24 hrs. apart[2]. A clinical diagnosis of pre-eclampsia includes proteinuria (300 mg or more of urinary protein during 24 hrs period) and edema (swelling of hand and feet) arising in the second half of the pregnancy in a previously normotensive women[3]. Importantly, the pregnancy induced hypertension was differentiated into two subgroups (mild and severe)[4]. An immunological disturbance causes abnormal placental implantation resulting in decreased placental perfusion. This abnormal placental perfusion stimulates the production of substances in the blood that activate, injure the endothelial cells[5]. Pre-eclampsia is thought to be caused by shallowly implanted placenta which becomes hypoxic, leading to an immune reaction characterized by secretion of up regulated inflammatory mediators from the placenta and acting on the vascular endothelium [6].

Fibrinogen, a major heterogenous coagulation protein. It is a symmetrical glycoprotein with 3 main fractions—High molecular weight fibrinogen (HMW-fibrinogen), low molecular weight fibrinogen (LMW-fibrinogen) and low molecular weight' fibrinogen (LMW'-fibrinogen)[7]. Fibrinogen is not detected in the serum, since it is used during coagulation. Normal concentration of fibrinogen is in the range of 180-400 mg/dl in freshly stored oxalated plasma. Fibrinogen, produced in liver, is the primary material of fibrin [8].

Fibrinogen, F VII, F VIII, F IX and F X levels show a marked increase in normal pregnancy. Increasing thrombosis tendency compared to peers who are not pregnant caused pregnancy to be characterized as a prothrombic state [9]. In normal hemostasis vasculature, thrombocytes, plasma coagulation factors, fibrinolytic factors and inhibitors of fibrinolysis play an important role. When vascular injury occurs, vasoconstriction, thrombocyte plug and fibrin accumulation are formed. If the defect in the vascular wall is small, thrombocyte plug formation may be sufficient and when the defect is large, in that case fibrin coagulation is necessary. When the vascular wall is damaged, thrombocytes adhered and aggregated in this region and cytokines that secreted increase adhesion and aggregation of other thrombocytes to the region [10]. All of these events can continuously trigger a cycle of coagulation and fibrinolysis in pregnancy and complicated pregnancy with pre-eclampsia.

The hallmark of preeclampsia include increased vasoconstriction resulting in maternal hypertension and reduced uteroplacental blood flow, disturbed vascular endothelial integrity with increased vascular permeability, and activation of the coagulation cascade.

Material and method –

The study was conducted from 2009-2011 at Mahila Chikitsalaya Jawahar Lal Nehru Medical College and associated group of hospitals, Ajmer (Rajasthan). A total of 100 pre-eclamptic women were enrolled for this study out of these 50 subjects were mild pre-eclamptic and 50 were severe. The results were compared with 50, age and parity matched healthy pregnant women. All subjects were primigravidas and their gestational ages were ranging from 28-40 weeks.

Mild pre-eclampsia defined by the American College of Obstetrics and Gynecology (ACOG; 2002) criteria as: (1) Blood pressure > 140/90 mmHg for two readings 6 hours apart; (2) Proteinuria > 300 mg/24 hours or +1 dipstick; (3) Edema.

Severe pre-eclampsia defined by American College of Obstetrics and Gynecology (ACOG; 2002) criteria as:
(1) Blood pressure > 160/110 mmHg for two readings 6 hours apart; (2) Proteinuria > 5 gm/24 hours or +2, +3 dipstick; (3) Serum creatinine > 1.2 mg/dl; (4) Platelets < 100,000/mm3; (5) Microangiopathic hemolysis; (6) Elevated liver enzymes; (7) Intrauterine growth retardation (IUGR); (8) Pulmonary edema. Exclusion criteria were Multiple pregnancy, Chronic hypertension, Premature rupture of membranes or clinical chorioamnionitis, Symptomatic inflammatory diseases, Diabetes Mellitus and Chronic renal disease.

The local ethics committee approved this study. Verbal consent has been taken from patients after explaining the

Volume : 5 | Issue : 10 | October 2015 | ISSN - 2249-555X

aim of this study.

Anthropometric Measurements:-
Height and weight were measured and BMI was calculated as kg/m2.

Biochemical Measurements:-
(1) Plasma fibrinogen concentration were measured by Von Clause A 1957 method [11].

(2)Mean arterial Blood pressure was determined by using the equation = (2 x diastolic + systolic) / 3 mmHg.

Statistical Analysis:-
Data are expressed as mean ± standard deviation. The means were compared using student's t- test. Pearson's correlation analysis was used for correlation of parameters measured. Analysis was two tailed and a p value ≤ 0.05 was considered statistically significant.

Result –
The Biochemical characteristics of the subjects are reported. The mean gestational age of healthy pregnant, mild pre-eclamptics and severe pre-eclamptics was 33.60 years, 34.28 years and 33.76 years respectively with age range from 28 to 40 years. The difference in mean gestational age of controls, mild and severe pre-eclamptics was non significant (p=0.4, p=0.7, p=0.3) table - 2.

Values of BMI in all subjects ranged from 18-43 kg/m^2 (mean ± standard deviation → 29.68 ± 5.41 kg/m^2, 30.08 ± 6.65 kg/m^2 and 29.88 ± 6.08 kg/m^2 respectively). These values did not show significant difference between controls, mild and severe pre-eclamptics (p= 0.3, p= 0.4, and p= 0.8 respectively).

The values (mean ± standard deviation) of biochemical parameters (1) Plasma fibrinogen in mg/dl → 313.00 ± 26.99, 360.36 ± 56.02, 379.32 ± 64.97 respectively (table -1); and (2) Mean arterial pressure in mmHg → 83.92 ± 12.17 , 115.16 ± 17.64 , and 133.12 ± 24.61 respectively (table - 1). Highly significant results were obtained on comparing mean arterial pressure and plasma fibrinogen values between different groups (healthy v/s mild, healthy v/s severe and mild v/s severe) (p < 0.001).

Table-1: Biochemical variables of different subject groups: -

Parameters	Healthy Pregnant Women	Mild Pre-eclampsia	Severe Pre-eclampsia
Fibrinogen (mg/dl)	313.00 ± 26.99	360.36 ± 56.02	379.32 ± 64.97
MAP(mmHg)	83.92 ± 12.17	115.16 ± 17.64	133.12 ± 24.61
Fibrinogen v/s MAP	r=0.05 p=0.30	r=0.27 p=0.002	r=0.15 p=0.07

MAP: Mean Arterial Pressure, r = Co-relation co-efficient, p= Pearson's co-efficient

Table-2: t and p values between different subject groups: -

Parameters	Healthy pregnant v/s Mild Pre- eclamptics		Healthy pregnant v/s Severe Pre-eclamptics		Mild pregnant v/s Severe Pre-eclamptics	
	t	p	t	p	T	p
Gestational Age (Years)	0.62	0.4	0.35	0.7	0.91	0.3
BMI(Kg/m2)	0.97	0.3	0.69	0.4	0.21	0.8
Fibrinogen (mg/dl)	6.86	0.00	8.31	0.00	2.35	0.20
MAP(mmHg)	15.07	0.000	17.37	0.000	5.99	0.000

Figure 1: Correlation of plasma fibrinogen (mg/dl) values with mean arterial pressure (mmHg) values in mild pre-eclamptics

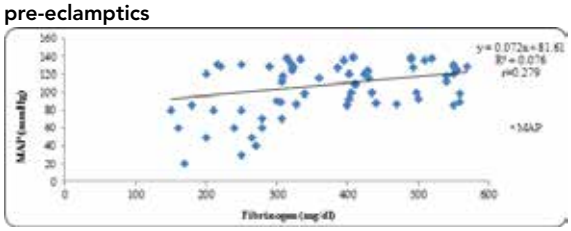
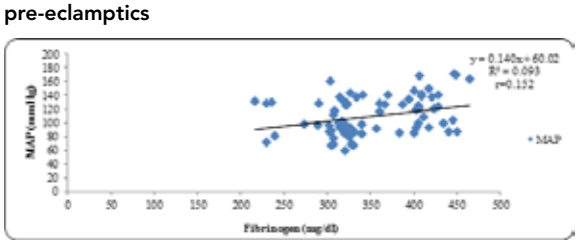


Figure 2: Correlation between fibrinogen (mg/dl) values and mean arterial pressure (mmHg) values in severe pre-eclamptics



In this study, a significant strong positive correlation was seen between fibrinogen and mean arterial pressure levels [r=0.2; p=0.002 two tailed] in mild pre-eclamptics and in severe patients [r=0.15; p=0.07two tailed]. There was a positive correlation between these parameters among healthy control group [r=0.05; p=0.30 two tailed] (fig. 1,2). The data of this study showed a strong association between plasma fibrinogen and mean arterial pressure reveals that hypertension and coagulation are linked process.

Discussion –
In the present study, mean arterial blood pressure level was significantly elevated in severe pre-eclamptics compared to mild pre-eclamptics (p<0.0001). These results emphasize that preeclampsia is characterized by hypertension. Preeclampsia appears likely that there are substances from the placenta that can cause endothelial dysfunction in the maternal blood vessels of susceptible women[12]. While blood pressure elevation is the most visible sign of the disease, it involves generalized damage to the maternal endothelium, kidneys, and liver, with the release of vasoconstrictive factors being secondary to the original damage. Therefore, monitoring of hypertension in pre-eclampsia will result in a significant improvement of many pathways supposed to be involved in pre-eclampsia complications.

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Patients with chronic hypertension have higher concentration of total fibrinogen. These patients also had higher concentrations of von Willebrand factor, a known marker for endothelial damage.

The toxemia syndrome, usually occurring in the third trimester of primigravidas includes hypertension, proteinuria, edema, consumptive coagulopathy, sodium retention and hyper-reflexia (pre eclampsia). In normal pregnancy, there is a hypercoagulable state with increased concentration of blood coagulation factors, decreased or unchanged concentration of blood coagulation inhibitors and impaired fibrinolysis. These changes increase with advancing gestation. In pre- eclampsia, these changes are exaggerated resulting in increased activation of the coagulation cascade and a more decreased fibrinolysis, associated with placental infarction and fibrin formation.

This study was carried out to examine the extent of inflammation in toxemia of pregnancy compared to healthy controls and also to evaluate the role of inflammatory markers in predicting severity of pre-eclampsia (both mild and severe).

Conclusion –

For the findings performed for this study, fibrinogen values were significantly elevated in mild & severe pre-eclampsia patients ($p<0.0001$) compared to healthy pregnant women. It plays a key role in platelet aggregation, the final step in coagulation cascade, through the formation of fibrin.

In the present study, we found a positive correlation between fibrinogen and mean arterial blood pressure levels in mild and severe pre-eclamptic women [$p=0.002$;$p=0.07$]. That shows there is a strong relationship between coagulation and hypertension which is a hallmark of pre-eclampsia.

Therefore, further understanding of the role of fibrinogen on trophoblast functions and pregnancy homeostasis can have significant impact in the prevention and treatment of obstetric complications of the pregnancy.

Thus, we are in need of a widely applicable and affordable test that could permit pre symptomatic diagnosis in order to identify and monitor the patients at risk and thus provide the best prenatal care for these women and their child.

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