

Fibronectin as an Early Predictor of Gestational Hypertension/Preeclampsia

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ABSTRACT

BACKGROUND

Hypertensive disorders complicate 2% to 8% of pregnancies globally. They are one of the leading causes of maternal mortality responsible for 16% of maternal deaths. Preeclampsia is a pregnancy specific syndrome whose pathophysiologic features have not been clearly established, but research during past two decades has suggested that maternal endothelial damage and improper placental development are involved in the genesis of preeclampsia. Fibronectin is known to be a marker of endothelial dysfunction, which occurs in early gestation in women who develop preeclampsia in later gestation and hence levels of fibronectin may vary in first trimester itself in such women. We wanted to examine the usefulness of single biomarker 'plasma fibronectin' in screening of pregnant women for gestational hypertension/preeclampsia, study the difference in fibronectin levels in early versus late onset gestational hypertension/preeclampsia and evaluate its levels in preeclampsia with severe features.

METHODS

200 antenatal women with singleton pregnancy, who were normotensive were enrolled in the study and plasma fibronectin levels were measured at 10-12 weeks of gestation. Women were followed throughout pregnancy and 12 weeks postpartum. Plasma fibronectin levels were compared between normotensive women and women who developed gestational hypertension/preeclampsia.

RESULTS

The mean values of plasma fibronectin are significantly higher in group who developed gestational hypertension/preeclampsia compared to group who remained normotensive (167+/-81 vs 114+/-58; p<0.05). The mean value in group with early onset disease as well as preeclampsia with severe features is higher than that of group with late onset disease and preeclampsia without severe features respectively. But the difference is not statistically significant.

CONCLUSIONS

Study showed that plasma fibronectin could be used as a marker for early prediction of gestational hypertension/ preeclampsia.

KEY WORDS

HDP, Gestational Hypertension, Preeclampsia, Fibronectin, Endothelial Dysfunction, Predictor

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BACKGROUND

Hypertensive disorders of pregnancy (HDP) complicate 2% to 8% of pregnancies globally¹. They are one of the leading causes of maternal mortality responsible for 16% of maternal deaths.^{1,2} Preeclampsia is a pregnancy specific syndrome whose pathophysiologic features have not been clearly established, but research during past two decades has suggested that maternal endothelial damage and improper placental development are involved in the genesis of preeclampsia. Maternal immunologic intolerance, maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy and numerous other maternal, paternal, and fetal factors like genetic, nutritional, and environmental factors have been implicated in its development.

Risk Factors

Primiparity, maternal age >35 years, pre pregnancy body mass index (BMI) >30, multifetal gestation, inter pregnancy interval >5years, diabetes mellitus, gestational diabetes mellitus (GDM), history of preeclampsia, antiphospholipid antibody syndrome (APLA)/ systemic lupus erythematosus (SLE), chronic hypertension, artificial reproductive techniques.³

Predictive Tests

Tests for placental perfusion, fetoplacental unit dysfunction markers, renal dysfunction markers and various indicators of endothelial dysfunction like Platelet fibronectin, endothelial adhesion molecules, prostaglandin, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteine, lipids, antiphospholipid antibodies, plasminogen activator-inhibitor, leptin, p-selectin, angiogenic and anti-angiogenic factors which include placental growth factor, vascular endothelial growth factor, fms-like tyrosine kinase receptor-1, endoglin⁴.

Prevention

In women considered to be at risk based on clinical factors, low dose aspirin and calcium are recommended for prevention of PE by various international recommendations. Aspirin should be given in the 100-150 mg/day started preferably before 16 weeks, continued until delivery. Calcium supplementation of about 1.2-2.5 g/day is recommended for women with low calcium intake (<600 mg/day). Regular exercise during pregnancy has shown to lower the risk of developing preeclampsia.³

Fibronectin

Fibronectin belongs to family of high molecular weight glycoproteins that occurs in 2 forms. Soluble form plasma fibronectin (pFN) is synthesized by hepatocytes, and is involved in opsonic activity with reticuloendothelial system and in clot stabilization. Nonsoluble form cellular fibronectin is synthesized by fibroblasts, endothelial cells, macrophages and astroglial cells, Schwann cells, chondrocytes, myoblasts, certain epithelial cells including those derived from carcinoma cell lines and is involved in cell adhesion, migration, growth and differentiation.⁵⁻¹² Fibronectin is found to increase in various conditions like collagen vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, ischemic heart disease, some cancers, trauma. In 1986, Hess LW¹³ found

that plasma concentrations of fibronectin rose significantly throughout pregnancy, and at six weeks postpartum levels were similar to those observed at the time of delivery, returned to nonpregnant levels by eight months postpartum.

PE is characterised by generalised dysfunction of maternal endothelium, as demonstrated by increased levels of factor VIII, total and cellular fibronectin, thrombomodulin, endothelin, growth factor activity, and a disturbance of tissue plasminogen activator inhibitor-1 and prostacyclin/thromboxane A2 balance¹⁴. Since 1984, fibronectin has received attention, when Stubbs and Lazarchick reported its concentration to be elevated in PE patients.¹⁵ Aetiology of total fibronectin increase in PE remains uncertain, but several possibilities include amniotic fluid leakage into maternal circulation, increased hepatic fibronectin (acute phase reactant), endothelial cell damage (leakage), increased platelet production of fibronectin, increased tissue release of fibronectin secondary to vasospasm and hypertension, decreased renal clearance of fibronectin.

As the pathology behind PE starts well before the onset of clinical signs and symptoms, fibronectin could be released in circulation in higher levels during the initial stages of development of the disease and hence fibronectin levels are studied in first trimester and correlated with development of disease.

METHODS

It is a prospective observational analytical study conducted in Muslim maternity and children hospital, Hyderabad. All women attending obstetrics department of our hospital both inpatient and outpatient were booked. 95% of the women in the study population belong to middle and low socio-economic status and marriage at earlier ages. Most of them are from urban background. Study was conducted over a period of 2 years. Justified sample size for the study was calculated according to the formula minimum sample size (n) = Z²P (1-P)/ d². With prevalence of 15% in our setting, sample size required was 196. Hence 200 women were enrolled into the study. Patient information sheet was given and written informed consent was taken from the patients who are willing to participate and meet the criteria. Patients with singleton pregnancy who are in the first trimester were included in the study. Patients with chronic hypertension, chronic kidney disease, autoimmune diseases such as SLE and APLA, hyperthyroidism and other endocrinal diseases were excluded from the study.

Once the patients entered into the study, detailed history was taken, examination was done. Gestational age was confirmed by antenatal scan. All preliminary and baseline investigations like complete blood picture, complete urine examination, oral glucose challenge test, blood grouping, thyroid profile was done. 2 drops of capillary blood was collected by lancet on filter paper for measurement of plasma fibronectin at 10-12 weeks of gestation. In lab, serum proteins were measured using dried blood spot immunofluorometric assay supplied by PerkinElmer.

Patients received routine ANC every month up to 28 weeks, at 15 days interval up to 32 weeks, following which they came weekly for ANC. All these women were followed

throughout their pregnancy, labour & 12 weeks postpartum for the development of signs and symptoms of GHTN/PE. Those cases developing GHTN/PE were evaluated fully with platelet count, renal function test, liver function test & ultrasound with Doppler. These cases were frequently followed closely and were evaluated fully so as to avoid the development of catastrophic complications and received antihypertensive therapy as necessary.

Statistical Analysis

Statistical evaluation is done using computer software SPSS 15.0 version statistical package. Chi square test/ Fisher exact test has been used to find the significant association of PE with fibronectin. All data is represented by mean and standard deviation. Student t test is done to know the significance of mean values. Pearson Chi-square values and P values are computed to compare risk factors, associations and complications of 2 groups.

RESULTS

Out of 200 women studied, 8 women had abortions, 4 women had anomalous fetuses and hence terminated, 18 women were lost for follow up. The remaining 170 women were followed till delivery and postpartum and results are available for analysis.

Group A

Women who developed GHTN/PE = 32.

Group B

Women who remained normotensive = 138.

Group A	167.81(98)	p= 0.0001
Group B	114.98(58.2)	
Non-Severe HDP	157.7(65.1)	p= 0.35
Severe HDP	184.6(97.7)	
Early onset HDP	178.88(98.7)	p= 0.38
Late onset HDP	153.57(41.72)	

Table 1. pFN Levels in µg/dL Mean (SD)

Percentile	pFN (µg/ml)
25 th	76
50 th	110
75 th	154
Cent	376

Table 2. Quartile Distribution of pFN Levels

		Quartile				Total	χ ² = 16.90007 P=0.0007
		1 st	2 nd	3 rd	4 th		
Group A	Count	1	3	4	8	16	
	%	6.3%	18.8%	25.0%	50.0%	100.0%	
Group B	Count	20	18	17	14	69	
	%	28.9%	26.09%	24.7%	20.3%	100.0%	
Total	Count	21	21	21	22	84	
	%	26.2%	23.8%	25.0%	25.0%	100.0%	

Table 3. Distribution of Groups in 4 Quartiles

DISCUSSION

The mean (SD) values of pFN in this study is 124.14(65.72). The values obtained in current study are low compared to other studies.¹⁶⁻¹⁹ The difference may be due to-

1. Differences in age distribution. The mean age of subjects in this study is 23.4 years.
2. Risk category of population enrolled. This is a study on all pregnant women who attended our antenatal OP during that period.
3. Inclusion and exclusion criteria used.
4. Hospital setting. This is a study in secondary care centre.
5. Demographic profile of population. Subjects mostly belonged to middle and low socioeconomic class.
6. Racial variation. Our subjects are Asians. (other studies were in western population)
7. Gestational age: this study is at 10-12 weeks of gestation.
8. Use of low dose aspirin prophylaxis.(no such use in other studies)
9. Method of sampling and estimation. pFN levels are measured from capillary blood sample by dried blood spot technique and analysed by immunofluorometric assay supplied by PerkinElmer. (other studies used enzyme linked immunosorbent assay, nephelometric assay)

The mean values of pFN are significantly higher in group A compared to group B (167+/-81 vs 114+/-58; p<0.05). The mean value in group with early onset GHTN/PE as well as PE with severe features is higher than that of group with late onset GHTN/PE and PE without severe features respectively. But the difference is not statistically significant. pFN levels are significantly higher in obese overweight subjects compared to normal BMI subjects (150+/-58 vs 110+/-63; p<0.05). This evidence may add to the relative risk of PE in obese women. Four women in this study developed diabetes during pregnancy. The levels of fibronectin in these women are very much higher than those of nondiabetic women. The mean is almost doubled (216+/-92 vs 119+/-60). This can be related to underlying common pathology of endothelial dysfunction in diabetes and PE. The quartile distribution table shows that 50% of group A subjects are above 75th percentile (pFN= 154 µg/ml) compared to 20% of group B subjects showing a significant difference (p<0.05).

As the pFN value of 75th percentile is 154 µg/ml, if 154 is taken as cut-off, Sensitivity (Sn) is 50%, Specificity (Sp) 82.6%, Positive Predictive Value (PPV) is 40%, Negative Predictive Value (NPV) is 87%, Positive Likelihood Ratio (PLV) is 2.77, and Negative Likelihood Ratio (NLR) is 0.60. This efficacy is comparable to the Sn of 55% in a recent study 2014, by using maternal factors, ultrasound parameters – uterine artery notching, serum markers – pregnancy associated plasma protein A (PAPPA), beta human chorionic gonadotropin (β HCG) for the first trimester screening of early onset preeclampsia.²⁰

CONCLUSIONS

Plasma fibronectin showed high specificity and higher levels of plasma fibronectin indicated stronger evidence for the disease and its complications. Its high negative predictive value is a supportive guide against the development of the disease within next few weeks. However, this test shows a low sensitivity, costs around 3000 - 5000 rupees and is not widely

available in India. Hence, a single 1st trimester measurement of plasma fibronectin cannot be used as a screening tool for GHTN/PE in general population. However, it could be recommended in high risk population to help to determine relative risk for developing GHTN/PE, for close follow-up and better management.

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