

The Value of Determinating Plasma Fibronectin Concentration in the Early Diagnosis of Pre-eclampsia

PRE-EKLAMPSİ ERKEN TANISINDA PLASMA FİBRONEKTİN KONSANTRASYON TAYİNİNİN ÖNEMİ

Dr.Cemil AKGÜL*, Dr.Nihal SALMAYENLİ**, Doç.Dr.Lemi İBRAHİMOĞLU*, Prof.Dr.Ahmet SİVASLI**, Dr.Fevzi ÇİZMECİOĞLU***

İstanbul Üniversitesi İstanbul Tıp Fakültesi *Kadın Hastalıkları ve Doğum ABD, **iç Hastalıkları ABD, ***Halk Sağlığı ABD, İSTANBUL

SUMMARY

Concepts about the pathogenesis of pre-eclampsia especially involve endothelial cell damage. Increase in arterial blood pressure in pre-eclampsia seems to be in an association with a preceding rise in plasma fibronectin levels, perhaps contributing to endothelial disruption. Plasma fibronectin levels were measured in 30 healthy normotensive women and in 38 pre-eclamptic patients. Fibronectin concentrations were significantly higher in pre-eclamptic cases ($t: 8.71, p<0.001$) and in 7 normotensive women whom 6 of them developed hypertension with proteinuria and/or edema. Fibronectin levels increased 30 ± 8.7 days earlier than the onset of hypertension. It is to be concluded that fibronectin elevations must warn clinicians for its predictive role especially in pre-eclampsia.

Key Words: Pregnancy, Fibronectin, Pre-eclampsia

Anatolian J Gynecol Obst 1993, 3:10-12

Fibronectin is a group of glycoprotein and a principal component of the extracellular matrix which is thought to maintain the integrity of the microvasculature and reticuloendothelial system. Opsanization, cell adhesion, tissue repair, oncogenic transformation phagocytosis and coagulation are some of its functions (1,2). Normal levels range from 200-400 u gr/ml (3). Although it is reported that levels of fibronectin remain to be unchanged during pregnancy (4), there are published investigations which notify the elevations espe-

Geliş Tarihi: 31.01.1992

Kabul Tarihi: 23.06.1992

Yazışma Adresi: Dr.Cemil AKGÜL
İstanbul Üniversitesi, İstanbul Tıp Fakültesi,
Kadın Hastalıkları ve Doğum ABD, İSTANBUL

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ÖZET

Pre-eklampsi patogenezindeki görüşler, özellikle endotelial hücre harabiyeti üzerinde yoğunlaşmaktadır. Pre-eklampside kan basıncında görülen artış; fibronektin düzeylerindeki, muhtemelen endotelial harabiyet ile ilgili olan ve daha önceden saptanabilen yükselme ile ilişkili olsa gerektir. Bu çalışmada 30 sağlıklı normal gebe ve 38 pre-eklampsi olgusunda plasma fibronektin düzeyleri 67-çümlenmiştir. Pre-eklamptik olgularda ve daha önce normotensif olan 7 olgunun sonradan hipertansiyon gelişen 6'sında fibronektin düzeyleri anlamlı derecede yüksek bulunmuştur ($t: 8.71, p<0.001$). Bu yükselme hipertansiyon gelişiminden 30 ± 8.7 gün önceden tesbit edilmiştir. Bu nedenle gebelikte fibronektin konsantrasyonlarından herhangi bir yükselme, özellikle hipertansif bir hastalığın gelişimi açısından klinisyeni uyarmalıdır.

Anahtar Kelimeler: Gebelik, Fibronektin, Pre-eklampsi

T Klin Jinekoloj Obst 1993, 3:10-12

daily at the third trimester (1,5). Although the plasma concentration and tissue distribution is altered during diseases, no specific illnesses have been categorized which result in qualitative or quantitative abnormalities in fibronectin levels.

The present study is designed for investigating fibronectin levels during normal and pre-eclamptic pregnancies and to assess its predictive value in gestational hypertensive disorders.

MATERIALS AND METHODS

This study was conducted on a total number of 68 women seen at the outpatient clinic of the Department of Obstetrics and Gynecology of Istanbul Faculty of Medicine. After giving informed consent to all patients the study was prospectively continued between

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January 1990 and June 1991. The blood pressure was measured in the sitting position. Gestational hypertension was defined as a diastolic blood pressure of > 90 mmHg on at least two occasions during the second half of pregnancy in a previously normotensive woman. Gestational proteinuria was accepted as > 300 mg proteinuria/day (6).

The patients were designed in two groups. First of all; plasma fibronectin levels were established in a group of 38 pre-eclamptic patients and 3 of those were eclampsia cases. As a second group 30 uncomplicated pregnant women with a gestational age greater than 20 weeks were selected during their antenatal visits. During the time fibronectin measurement were being done; none of the patients had been operated, had blood transfusions or had experienced gross trauma within 5 months. This group of pregnant women was followed till delivery in order to see whether pre-eclampsia develops in patients with previous high fibronectin levels or not and also to see the fate of pregnancies with normal fibronectin concentrations.

Measurement of fibronectin concentrations were done in the Central Biochemistry Laboratory of Department of Internal Medicine. For this purpose 10 cc of venous blood sample was drawn into heparinized glass tubes from each patient. By centrifugation at 2000 g for 15 minutes platelet-poor plasma was obtained. It was stored at -70°C unless assayed that day for fibronectin.

The concentration of fibronectin determined quantitatively by Behring's immunodiffusion plates. Plates coated with agarose gel, involve antiserum specific to fibronectin in their hollows and 20 µl of serum were added to those hollows. After the antigen-antibody reaction, between fibronectin and antiserum, the diameter of precipitation circles were measured with ocular and those diameters were matched with the graphics drawn before. The assay range of the plates were 25-400 mg/dl. Fibronectin levels above those values were studied by dilution of the specific serum with 1/10 physiologic serum and the established values were multiplied by 10. Results obtained, were evaluated by Student's modified t test and reported as mean ± SD.

RESULTS

The results of the pre-eclamptic group are summarized in Table 1. The mean plasma fibronectin concentration was 606.5 ± 228 µg/l. There were 3 cases of eclampsia in this group.

In the second group; among 30 pregnant women, pre-eclampsia developed in 6 patients (Table 2). In this subgroup, fibronectin levels increased 30 ± 8.7 days before the onset of hypertension (Table 3). Other 24 patients, in this group, had uneventful pregnancies

Table 1. Levels of fibronectin concentrations in pre-eclamptic patients

Case Number	Fibronectin Concentration Levels (µg/ml)	Case Number	Fibronectin Concentration Levels (mg/ml)
1	636	23	1090
2	438	24	800
3	312	25	640
4	288	26	768
5	606	27	760
6	846	28	268
7	570	29	860
8	504	30	1060
9	654	31	336
10	336	32	750
11	606	33	660
12	822	34	768
13	654	35	714
14	726	36	274
15	468	37	672
16	288	38	312
17	480	39	552
18	250	40	780
19	476	41	918
20	160	42	822
21	660	43	654
22	512	44	936

Table 2. Levels of fibronectin concentrations in a group of 30 antenatal patient

Normotensive group	Fibronectin Concentration Levels (µg/ml)	Date of Sampling	Date of Delivery
1	250	07.11.90	12.12.90
2	202	07.11.90	15.01.91
3	224	01.12.90	27.12.90
4	294	17.01.91	02.03.91
5	320	02.06.90	27.09.90
6	268	02.03.91	05.05.91
7	268	13.01.90	24.02.91
8	342	03.02.91	17.02.91
9	250	29.05.91	21.09.91
10	336	27.02.91	11.03.91
11	274	13.01.91	24.02.91
12	552	10.03.91	20.04.91
13	250	03.11.90	21.01.91
14	256	07.11.90	02.02.91
15	282	15.11.90	16.02.91
16	320	05.12.90	16.03.91
17	230	23.12.90	27.01.91
18	208	17.02.91	20.03.91
19	242	14.02.91	30.03.91
20	268	02.06.90	14.06.91
21	320	23.02.91	13.03.91
22	208	17.02.91	20.04.91
23	300	05.05.91	18.05.91
24	268	27.01.91	23.03.91
Pre-eclamptic group	Fibronectin Concentration Levels (µg/ml)	Date of Sampling	Date of Delivery
25	552	17.02.91	09.03.91
26	760	21.02.91	20.03.91
27	918	27.02.91	04.04.91
28	822	02.03.91	14.04.91
29	654	14.03.91	05.04.91
30	936	12.01.91	13.02.91

Normotensive women (n=24), Pre-eclamptic women (n=6)

during the remaining time after sampling and the mean fibronectin level was 281 ± 70 µg/ml.

Table 3. Time interval between the date of sampling and clinical diagnosis of pre-eclampsia

Fibronectin Concentration Levels (mg/ml)	Time Interval (day)
552	20
780	27
918	36
822	43
654	22
936	32
N-6	
Mean-30 ± 8.74 days	

Table 4. Statistical significance of measurement of fibronectin levels predicting pre-eclampsia

Pre-eclampsia	Present	Absent	Total
Fib. > 400 ug/ml	6	1	7
Fib.<400 ug/mlO	23	23	
Total	6	24	30
Sensitivity: 1.00		NPV: 1.00	
Specificity: 0.96		FPR: 0.14	
PPV: 0.86		FNR: 0.00	

A total number of 68 patients; 44 cases of pre-eclampsia and 24 cases of normal pregnancies were evaluated in this study. The difference for fibronectin levels between the two groups was significant; $t:8.71$, $p<0.001$. Statistical evaluation of fibronectin concentrations in antenatal patients is summarized in Table 4.

Among 44 pre-eclamptic patients, 4 cases of eclampsia occurred. The difference between the levels of fibronectin concentrations among the preeclamptic and eclamptic cases was not significant; $t: 0.587$, $p>0.05$.

DISCUSSION

Why one confronts with high fibronectin concentrations in preeclamptic cases is an enigma. Elevated plasma levels of fibronectin are not simply the result of increased blood pressure but reflect a maternal derangement specific to pre-eclampsia (7). A decrease in metabolism or excretion, or an abnormally high release of fibronectin to plasma could explain the mechanism (3).

Perhaps due to an abnormal prostaglandin action; vascular endothelial integrity breaches and fibronectin, between the vascular endothelium and basement membrane, gets into blood stream (3,8,9,10). Degenerative changes, up to periportal necrosis could be seen in eclamptic cases. As fibronectin production by hepatocytes should not be effective in plasma fibronectin concentrations, other body tissues must be considered as the source of its rise.

Fibronectin levels in normotensive pregnancies and preeclamptic cases and the statistical significance of the difference obtained in this study ($p<0.001$) are almost in consistency with those established by Stubbs and Lazarchick (3,9).

Lazarchick and Ballegeer (9,11) detected high levels of fibronectin before the onset of hypertension, >4 weeks and 3.6 ± 1.9 weeks before, respectively. In this study preeclampsia developed 30 ± 8.7 days after the establishment of high levels with a sensitivity of 100% and specificity of 96% and a predictive value of 86%.

Although it is not possible to explain the rise with the data obtained recently, it is to be emphasized that a vascular endothelial disorder exists in its pathogenesis and high levels of fibronectin concentrations seem to be a strong forrunner of disaster in normotensive women destined to be pre-eclamptic late in pregnancy.

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