Assessment of the Role of Fibrinogen in Preeclampsia

Fibrinojenin Preeklampsideki Rolünün Değerlendirilmesi

Gökhan Açmaz, MD.
Department of Obstetrics and Gynecology,
Erciyes University, Medical Faculty.
gokhanacmaz@mynet.com

Ahmet Tayyar, MD.
Department of Obstetrics and Gynecology,
Erciyes University, Medical Faculty.
ahmet_tyyr@yahoo.com

Mehmet Tayyar, MD.
Department of Obstetrics and Gynecology,
Erciyes University, Medical Faculty.
prtayyar@erciyes.edu.tr

Abstract
Purpose: Our aim was to detect the levels of fibrinogen in groups which were comprised on the basis of lung maturity and evaluate diagnostic value of fibrinogen in preeclamptic pregnants.
Materials and Methods: A total of 116 pregnant women between 26th and 40th weeks of gestation admitted to our department were investigated. Fibrinogen was measured in 63 pregnant women whose pregnancy was complicated with preeclampsia and in 53 pregnant whose gestation was uncomplicated. Patients were divided into two groups according to their gestational age on the basis of lung maturation. The first group constituted preeclamptic and healthy pregnant women whose pregnancies were between 26–33rd weeks of gestation. The second group constituted preeclamptic and healthy pregnant women whose pregnancies were between 34-40th weeks of gestation. Chi-square, Mann Whitney U test and Fischer exact tests were performed for comparison of means and/or medians.
Results: There was a statistically significant difference between preeclamptic and healthy pregnant (p=0.005) in first group. There was no statistically significant difference between preeclamptic and healthy pregnant (p=0.234) in second group. In collective examination there was statistically significant difference between preeclamptic and healthy pregnant (p=0.012).
Conlusions: Elevated levels of fibrinogen in healthy pregnancies and decreased levels of fibrinogen in preeclamptic patients were detected.

Key Words: **Pregnancy; Preeclampsia; Fibrinogen.**

Özet
Amaç: Sunulan çalışmanın amacı fetal akciğer maturasyonu esas alınarak oluşturulan gruplarda, fibrinojen seviyelerinin preeklampside tanısal anlamının olup olmadığını ortaya koymaktır.
Yöntem ve Gereçler: Erciyes üniversitesi tıp fakültesi kadın hastalıkları ve doğum Kliniğine başvuran 80 preeklamptik ve 70 sağlıklı gebe çalışmaya dahil edilmiş, çalışma 63 preeklamptik ve 53 sağlıklı gebe ile tamamlanmıştır. Akciğer maturasyonu esas alınarak, gebeler 26–33. gestasyonel haftalarda (birinci grup) ve 34–40. gestasyonel haftalarda (ikinci grup) fibrinojen açısından karşılaştırılmış, ardından istatistiksel analizler preeklamptik ve sağlıklı gebeler arasında topluca yapılmıştır.
Bulgular: Birinci grupta bulunan preeklamptik gebelerde fibrinojen değerleri, sağlıklı gebelerden ölçülenlere göre istatistiksel olarak anlamlı (p=0.005) derecede düşük bulunmuştur. İkinci grupta yer alan gebelerin fibrojen değerleri sağlıklı gebelerde ölçülenden farklı bulunmamıştır. Tüm preeklamptik gebelerin fibrinojen değerleri ise sağlıklı gebelerden istatistiksel olarak düşük bulunmuştur.
Sonuç: Fibrinojen değerleri gerek tüm preeklamptik gebelerle sağlıklı gebelerin karşılaştırılmasında gerekse 26-33. Gestasyonel haftalarda bulunan preeklamptik ve sağlıklı gebelerin karşılaştırılmasında düşük olarak bulunmuştur.

Anahtar Sözcükler: **Fibrinojen; Gebelik; Preeklampsi.**

Submitted : June 06, 2007
Revised : July 07, 2007
Accepted : January 17, 2008

Corresponding Author:
Gökhan açmaz, MD.
Department of Obstetrics and Gynecology,
Erciyes University, Medical Faculty
Kayseri, Turkey

Telephone : +90 352 4374937-20525
E-mail : gokhanacmaz@mynet.com

Introduction

Preeclampsia is a systemic disease characterized with hypertension, edema and proteinuria. Hematologic, genetic and immunologic play role in preeclampsia etiopathogenesis. Fibrin deposit in vascular and endothelial area of many organs and placenta is the most well known features of this disease. Preeclampsia is major causes of maternal morbidity and mortality in the world. Its frequency changes according to geographical regions but it is known that the rate is between 5–7% (1, 2).

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 (3). 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 (5, 6).

All of these events can continuously trigger a cycle of coagulation and fibrinolysis in pregnancy and complicated pregnancy with preeclampsia. Natural anticoagulants, are stimulated by the result of thrombosis formed during pregnancy. Some of them are protein C, protein S and antitrombin III (AT III). Main target of protein C and protein S is the F Va and F VIIIa on the intrinsic and extrinsic pathways. AT III demonstrates an anticoagulant effects, binding to thrombin in one-to-one rate. Therefore hemostasis is balanced and the body is protected from harmful effects of coagulation cascade (7, 8).

Heavy and atypical form of preeclampsia, the HELLP syndrome, is the result of the hypertension seen in pregnancy and reveals itself with hemolysis, increased liver enzymes, low platelet number. It is similar with disseminated intravascular coagulation syndrome. This is the major cause of morbidity and mortality of mother and baby. Its pathogenesis is not fully clarified. Increase in fibrin destruction products and decrease in fibrinogenesis are generally expected in HELLP syndrome (9).

Fibrinogen (factor I) is a major plasma protein and is the most important material of coagulation cascade. Blood coagulation does not occur in patients with afibrinogenemia or critical hypofibrinogenemia even though other coagulation factors are in normal limit (10, 11). 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 fresh stored oxalate plasma. Fibrinogen, it is produced in liver, is the primary material of fibrin (12).

The objective of this study is to demonstrate whether fibrinogen levels have a significant role or not in diagnosis of preeclamptia, regarding physiologic changes and fetal lung maturation in pregnancy.

Materials and Methods

Eighty preeclamptic or eclamptic patients and 70 healthy pregnant women between 26-40 weeks (18 – 43 years of age) who admitted to Erciyes University Medical School Department of Obstetrics and Gynecology were included in the study. A total of 116 participants (63 patients in the study group and 53 pregnant women in control group) could complete the study. This study was carried out after taking approval of Erciyes University Ethical Committee and in accordance with Helsinki declaration. Information had been given to all patients and their written consent was taken.

Exclusion criteria were multiple pregnancy, chronic renal or vascular disease, thromboemboli history, anticoagulant or non-steroid anti-inflammatory drug use and smoking in both control and study groups.

Preeclamptic and healthy pregnant women who participated in the study were divided into two subgroups regarding their pregnancy weeks: Group I: 26–33 weeks and Group II: 34–40 weeks. In all subjects, hemoglobin, platelet, aspartat aminotransferase (AST), alanin aminotransferase (ALT), lactate dehydrogenize (LDH), blood urine nitrogen (BUN), creatinin (Cre), fibrinogenesis levels, blood group analysis and cross comparison were investigated. With urine stick, proteinuria was also evaluated. In each group, age, fetal loss, 1st minute and 5th minute Apgar scores and fibrinogen levels of preeclamptic pregnant women were compared with those of healthy pregnant women. A comparison was also performed between the patient and control groups without regarding the pregnancy week.

Preeclampsia diagnosis was made based on the criteria published in 2000 version of "National High Blood Pressure Education Program Working Group of National Institutes of Health (NIH)". These criteria are as follows: (1) pregnancy week 20 or more (2) blood pressure 140/90 mmHg or above measured after a five-minute-period of resting and also in the following six hours (3) proteinuria >300 mg/day or 2+ proteinuria in urine stick and (4) 1+ pretibial edema following 24 hours resting. Pregnancy week was calculated from last menstruation date (LMD) and afterwards the pregnancy week was approved with ultrasanography (USG). When there are discordance more than two weeks between calculated and determined with ultrasonography or patients can not remember their LMD accurately, previous USG information was required and fetal development was also evaluated with USG.

Indications for emergency labour were eclampsia, non-controlled hypertension, serious headache and visual disorders, levels of platelet lower than 100.000 mm^3, elevated liver enzymes more than twice, deterioration of kidney function tests, epigastric pain, serious bleeding and presence of deceleration in non stress test (NST). Pregnant woman under 34th gestational week were monitorized and measured daily amnion volume and NST in the lack of one of above-mentioned emergency labor indications. Betametazone in dose of 24mg administered twice daily was administered intramuscularly in order to provide lung mutation and gain time at least one week.

Fibrinogen was studied using coagulometer device with ERCEP bioMerieux (Durham/North Carolina/USA) kit in Dedeman Oncology Hospital, Medical Faculty, Erciyes University (MDA II Platelin LS, Durham/North Carolina/USA) and fibrinogen values were given as mg/dl.

Conformity of constant variables to normal distribution was tested with Kolmogorov-Smirnov test. Data were given as mean, median, minimum, maximum, and standard deviation. Continuous variables were compared using Mann Whitney U test and categorical variables were compared using chi-square test between control and preeclamptic groups. The significance level was $p<0.05$. Statistical analysis was performed using SPSS 13.0 (Statistical Packages for Social Sciences; SPSS Inc., Chicago, Illinois, USA).

Results

Thirteen of 28 (44%) preeclamptic pregnant were primipar and 15 (53.6%) multipar; 11 (44%) of 25 healthy pregnant was primipar and 14 (56%) multipar in 26–33. gestational weeks. 10 (28.65) of 35 preeclamptic pregnant was primipar and 25 (71.4%) multipar; 8 (28.6%) of 28 healthy pregnant was primipar and 20 (71.4%) multipar in 34-40 gestational week. No statistically significant difference was found between the groups (p=0.319). When gestational week was not taken into consideration, 19 (35.8%) of 53 pregnant in control group was primipar and 34 (64.2%) multipar; 23 (36.5%) of 63 patients in experimental group was primipar and 40 (63.5%) multipar. When groups were compared in terms of gravida and parity values, no statistical difference was found (p=0.095).

The details of age, Apgar score, fetal loss, birth weight and fibrinogen values were given in Table I. No statistically significant difference was documented in terms of age (p=0.929) and fetal loss (p=0.378) between preeclamptic and healthy pregnant women in gestational week 26-33. However, birth weight ($p<0.001$), apgar scores at minute one and five were statistically different in preeclamptic and healthy pregnant women ($p<0.001$). No statistical difference was observed in terms of age (p=0.309) and fetal loss (p=0.423) between preeclamptic and healthy pregnant women in gestational 34-40 week. However, birth weight ($p<0.001$), apgar in the first (p=0.002) and fifth minutes (p=0.002) were found to be statistically different between preclamptic and pregnant women.

Fibrinogen values were found to be significantly lower in preeclamptic group when compared to those of the control group at week 26-33 (p=0.005). Fibrinogen values were not found to be statistically different in preeclamptic group than control group at 34-40 week gestational age (p=0.234).

When healthy and preeclamptic pregnant women were compared without looking at their weeks, age (p=0.411) and fetal loss (p=0.234) values were not found statistically significant. However, birth weight ($p<0.001$), apgar scores in the first ($p<0.001$) and fifth ($p<0.001$) minutes and fibrinogen values (p=0.012) were found to be statistically significant (Table II).

Table I. Data revealing the comparison of healthy and preeclamptic pregnant women according to two different gestational weeks in terms of age, Apgar scores, fetal loss, birth weight and fibrinogen values.

Gestational Week	26-33 weeks		34-40 weeks	
	Control (n=25)	Preeclampsia (n=28)	Control (n=28)	Preeclampsia (n=35)
Age (year)				
x±sd	27.72±5.84	27.864± 5.63	28.04±5.52	29.72± 6.93
Median	27.00	26.00	27.50	32.00
Min-max	20.00-42.00	19.00-41.00	20.00-43.00	18.00-40.00
Apgar, 1 min				
x±sd	7.40±1.47	4.14±2.22*	7.68±0.99	6.09±2.44**
Median	8.00	4.00	8.00	8.00
Min-max	2.00-8.00	(0.00-8.00	4.00-8.00	0.00-8.00
Apgar, 5 min				
x±sd	9.36±1.63	5.71±2.69*	9.68±0.98	7.89±2.82**
Median	10.00	6.00	10.00	10.00
Min-max	3.00-10.00	0.00-10.00	6.00-10.00	0.00-10.00
Fetal loss				
x±sd	0.24±0.6	0.29±0.46	0.21±0.42	0.63±1.9
Median	<0.001	<0.001	<0.001	<0.001
Min-max	0.00-2.00	0.00-1.00	0.00-1.00	0.00-11.00
Birth weight (g)				
x±sd	3265.2±486.33	1470.54±535.18*	3309.29±553.61	2730.57±757.16 *
Median	3250	1430	3430	2870
Min-max	2000-4230	640-3000	1850-4300	(710-3900
Fibrinogen (mg/dl)				
x±sd	447.70±99.74	355.95± 99.18***	504.89±110.37	476.48±120.94
Median	403.74	338.92	514.87	457.00
Min-max	311.19-655.93	168.00-508.00	314.60-716.82	837.30-281.00

*p<0,001 **p<0,002 ***p<0,005

Table II. Data revealing the comparison of healthy pregnant women and preeclamptic patients in terms of age, Apgar score, fetal loss and birth weight without taking into consideration the week.

	Contol Group	Preeclamtic Group	p=
Age (year)			0.411
x±sd	27.89±5.67	28.94±6.40	
Median	20.00	28.00	
Min-max	20.00-43.00	18.00-41.00)	
Apgar, 1 min			<0.001
x±sd	7.55±1.23	5.22±2.52	
Median	8.00	6.00	
Min-max	2.00-8.00	0.00-8.00	
Apgar, 5 min			<0.001
x±sd	9.53±1.32	6.92±2.95	
Median	10.00	8.00	
Min-max	3.00-10.00	0.00-10.00	
Fetal loss			0.234
x±sd	0.23±0.51	0.48±1.45	
Median	<0.001	<0.001	
Min-max	0.00-2.00	0.00-11.00	
Birth weight (g)			<0.001
x±sd	3288.49±518.45	2170.56±915.13	
Median	3350.00	2100.00	
Min-max	1850.00-4300.00	640.00-3900.00	
Fibrinogen (mg/dl)			0.012
x±sd	477.91±108.38	422.87±126.32	
Median	474.18	424.72	
Min-max	311.19-716.82	168.00-837.30	

Discussion

Preeclampsia and eclampsia are major health problems in developing countries. High mother-baby mortality emphasizes the importance of the problem (2). For the diagnosis of preeclampsia and eclampsia, numerous tests may be used; however, it is a point of discussion whether fibrinogen should be used in diagnosis or not.

There is different information in literature about how does fibrinogen level change with relation to gestational week and its amounts measured in preeclamptic pregnant women. Madry et al (13) measured 370 mg/dl of fibrinogen levels in weeks 16–18 and 440 mg/dl in week 37 in healthy pregnant women. Kasper et al. (14) found fibrinogen concentration in normal pregnancy in second trimester 335 mg/dl and in third trimester to be 432 mg/dl. In the present study, fibrinogen level was found to be 447.70 mg/dl at 26-33 week and 504.89 mg/dl at 34-40 week and 477.91 mg/dl at 26-40 week in healty pregnant women. Higher levels of fibrinogen than other papers may be due to all healthy pregnant women including the study are in 3rd trimester.

In literature, the results from studies in which fibrinogen levels were compared between preeclamptic and healthy pregnant women are not compatible with each other. Scott and Worley (15) reported that there was no significant difference in some coagulation factors including fibrinogen and that there was only decrease in number of thrombocyte as selectively in preeclamptic and eclamptic patients. Vicdan et al. (16) found the level of 412.2 mg/dl fibrinogen in preeclamptic and eclamptic pregnant women and 439.2 mg/dl in control group. Pritchard el al. (17) reported that there was no statistically significant difference in maternal plasma fibrinogen values in the 20 healthy and 92 eclamptic pregnant women (415 mg/dl and 412 mg/dl, respectively). Schjetlein et al. (18) claimed that fibrinogen values were getting significantly lower because of the consumption coagulopathy pregnant women with preeclampsia and especially those with HELLP syndrome. Contrary to these findings, Üstün et al (19) showed that there was significant difference amongst preeclamptic group, non pregnant subjects and the healthy pregnant group and that the most marked elevation of fibrinogen level was in preeclamptic group. Since preeclampsia is a systemic inflammation, there might have been an increase in release of fibrinogen as a response to this inflammation.

In the present study, fibrinogen levels were found to be significantly lower in preeclamptic pregnant women than those of healthy pregnant between 26-33 weeks. This finding is in accordance with the findings of Schjetlein et al (18). However, in pregnancy weeks of 34–40, fibrinogen levels were not statistically significantly different between preeclamptic and control groups.

Changing levels of fibrinogen may result from two factors: First, preeclampsia is a systemic inflammation and fibrinogen, an acute phase reactant, are increased in response to inflammation (19). The second, in healthy pregnant women, fibrinogen level are increased by inflamation however, since compensatory coagulation and fibrinolysis is become exaggerated in preeclampsia, consumption coagulopathy occurs and fibrinogen level are returned to normal values (18). In our study, presented all healthy and preeclamptic pregnant women were in third trimester. For this reason, in the present study, increased fibrinogen levels in control group and decreased levels in preeclamptic pregnant women may be the consequence of consumption coagulopathy. In this regard, we believe that especially in severe preeclamptic patients, fibrinogen may have a diagnostic meaning.

Incompatible results in literature may be due to the different criteria accepted for preeclampsia, insufficient evaluation of groups in terms of inflammation, different inclusion and exclusion criteria and not taking into account non-inflammatory conditions such as early labor action during blood sample taking. Further larger studies are needed in order to investigate the role of fibrinogen levels in above-mentioned issues.

Kaynaklar

1.Davies JA. Prentice JRM. Coagulation chances in pregnancy – induced hypertension and growth restriction. In: Greer IA. Turpie AGG. Forbes CD. Editors. Haemostasis and Thrombosis in Obstetrics and Gynecology. London: Chapman & Hall; 1992. p.143–162.

2.Duley L. Maternal mortality associated with hypertansive disorders of pregnany in Africa, Asia, Latin America and Carribean. Br J Obstet Gynaecol 1992;99:547-553.

3.Ku DH, Arkel YS, Paidas MP. Circulating levels of inflammatory cytokines (IL-1 beta and TNF-alpha), resistance to activated protein C, thrombin and fibrin generation in uncomplicated pregnancies. Thromb Haemost 2003; 90: 1074–1079.

4.Vormittag R. Pabinger I. Thrombophilia and pregnancy complications. Hamostaseologie 2006; 26: 59–62.

5.Rodgers GM. Thrombosis and antithrombotic therapy In: Lee GR. Foerester J. Lukens J. Pine JW, editors. Wintrobe's clinical haematology. USA New Hampshire: Willams and Wilkins; 1999. p.1781-1791.

6.Menteş G. Ersöz B. Plazma proteinleri immünglobülinler ve pıhtılaşma faktörleri In: Dikmen N, Özgünen T, çeviri editörleri. Harper'ın Biyokimyası. İstanbul: Barış kitapevi; 1994. s.775–781.

7.Nicolaes GA, Dahlback B. Activated protein C resistance (FV (Leiden)) and thrombosis: factor V mutations causing hypercoagulable states. Hematol Oncol Clin North Am 2003; 17: 37–61.

8.Dati F, Pelzer H, Wagner C. Relevance of markers of hemostasis activation in obstetrics/gynecology and pediatrics. Semin Thromb Hemost 1998; 24: 443–448.

9.de Boer K, Buller HR, ten Cate JW, Treffers PE. Coagulation studies in the syndrome of hemolysis, elevated liver enzymes and low platelets. Br J Obstet Gynaecol 1991; 98: 42–47.

10.Sonnenwrt AC, Jarret L. Test of Blood Coagulation. Gradwohl's Clinical Laboratory Methods and Diagnosis. Eight edition. St. Louis. Toronto London: The CV Mosby company; 1980. p. 1013–1014.

11.Arthur C, Guyton MD: Textbook of medical physiology. Philadelphia: WB Saunders Co; 1976. p.169.

12.Muray RK, Mayer PA, Granner DK, Rodwell VW. Harper's Biochemistry Plasma proteins, immunoglobulins, Clotting factors. Twenty-second Edition. California 1991, pp: 610-22.

13.Madry JT. Blood coagulation defects during pregnancy. Obstet Gynecol 1962; 20:232-237.

14.Kasper CK, Hoag MS, Aggeler PM, Stone S. Blood clotting factors in pregnancy: Obstet Gynecol 1964; 24:242-247.

15.Scott JR, Worley RJ. Hypertensive disorders of pregnancy. In: Scott JR, Disaia FJ, Hammond CB, Spellacy WN, editors. Danforth's Obstetrics and. Gynecology, Sixth edition. Philadelphia: JB Lippincott Co; 1990. p. 411.

16.Vicdan K, Işık AZ, Akan H. Preeklampsi ve eklampside laboratuar bulgularının analizi. Maternal koagulasyon sistemindeki değişiklikler. Kadın-Doğum Dergisi 1992: 26–29.

17.Pritchard JA, Cunningham FG, Mason RA. Coagulation changes in eclampsia: Their frequency and pathogenesis. Am J Obstet Gynecol 1976; 124: 855-864.

18.Schjetlein R, Haugen G, Wisloff F. Markers of intravascular coagulation and fibrinolysis in preeclampsia: association with intrauterine growth retardation. Acta Obstet Gynecol Scand 1997; 76:541-546.

19.Ustün Y, Engin-Ustün E, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. Eur J Obstet Gynecol Reprod. Biol 2005;121:154–158.