Experimental
&
Clinical Article

The Relationship Between Proteinuria in Severe Preeclampsia and Maternal and Fetal Outcomes

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OBJECTIVE: To investigate if the degree of proteinuria is related to adverse pregnancy outcomes in preeclampsia patients.

STUDY DESIGN: The records of 129 severe preeclampsia, 11 eclampsia and 21 HELLP patients delivered before the 37th gestational weeks in Baskent University Adana Research Center between December 2005 and December 2011 were reviewed retrospectively. Group I (n=118) had proteinuria of less than 5g /24 h and Group II (n=43) had proteinuria equal to or more than 5 g /24 hour. Data were analyzed with Student's t test, Chi-square test and correlations were made with Pearson correlation test. P<0.05 was considered statistically significant. SPSS for Windows (version 17.0; SPSS, Inc., Chicago, IL) was used for statistical analyses.

RESULTS: The patients in group II were significantly younger (30.6±6.27 vs. 27.9±6.25) (p=0.01) and delivered significantly earlier (33.6±3.9 vs. 32±3.3) (p=0.02). Group I patients had significantly more risk factors (16.9 vs. 2.3%) (p= 0.015). History of hypertension was also more common in group I (11 vs. 0%) (p= 0.023).

CONCLUSION: The patients with proteinuria of ≥ 5 g/24 hr were younger, delivered at an earlier gestational age and had risk factors less frequently.

Key Words: Preeclampsia, Proteinuria, Delivery

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Introduction

Pre-eclampsia is a major cause of maternal and fetal mortality and morbidity worldwide. It is a diverse, multiorgan related disease process occurring in up to 5%-8% of pregnancies after 20 weeks' gestation. Globally, pre-eclampsia and eclampsia account for 10%-15% of maternal deaths and preeclampsia is the third leading cause of maternal mortality following embolism and hemorrhage.[1] It can also lead to significant fetal morbidity and mortality, including an increased incidence of placental abruption, fetal growth restriction, and preterm delivery. Expedited delivery is recommended in cases of severe preeclampsia if the fetus is more than 34 weeks old [2,3] However, for fetuses less than 34 weeks old and absence of maternal organ dysfunction, expectant management is recommended in order to improve perinatal outcomes.[3-7]

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Preeclampsia is defined as hypertension appearing after the 20th gestational week and proteinuria exceeding 300 mg in 24 hour urine samples.[2] Proteinuria in pregnancy has been accepted as a hallmark of preeclampsia and an indicator of its severity. According to the Working Group,[3] proteinuria of greater than or equal to 2 grams is suggestive of severe preeclampsia and the American College of Obstetrics and Gynecology (ACOG) suggested that proteinuria of 5 grams or more in 24 hours indicates severe preeclampsia.[4] While severe preeclampsia is known to be related to adverse pregnancy outcomes, it is still debatable if the degree of proteinuria is positively correlated with the risk of adverse maternal and fetal outcomes. Therefore, we aimed to investigate if the degree of proteinuria is related to adverse pregnancy outcomes in preeclampsia patients and review the literature with regard to proteinuria and to help guide the management of preeclampsia patients.

Material and Method

In this study the records of 129 severe preeclampsia, 11 eclampsia and 21 HELLP patients followed up and delivered before the 37th gestational weeks in Baskent University Adana Research Center between December 2011 and December 2005 were reviewed retrospectively. Solely based on maternal criteria, preeclampsia was defined as systolic blood pressure of

≥140mmHg or diastolic blood pressure of ≥90mmHg on two measurements 6 hours apart appearing after the 20th gestational week and proteinuria (>300mg) in 24-hour urine samples. Severe preeclampsia was defined as systolic blood pressure of ≥160mmHg or diastolic blood pressure of ≥110mmHg on two measurements 6 hours apart, platelets of <120.000, AST of >45, ALT of >60 and eclampsia. IUGR was defined as a fetal weight below 10 percentile for gestational age with abnormal Doppler flow studies and was not included in our diagnostic criteria for severe preeclampsia. Women with preexisting medical conditions were included. Multiple pregnancies and term pregnancies were excluded.

All urine samples were collected on a 24 hour basis. When the need to deliver has emerged before completion of 24 hours, urine collection was continued after delivery. The patients were assigned into two groups according to the degree of proteinuria. Group I (n=118) had proteinuria of less than 5g /24 h and Group II (n=43) had proteinuria equal to or more than 5 g /24 hour. Weight gain was calculated by subtraction of weight before conception from weight before delivery. Serum markers were measured during the first trimester screening between 11-14 gestational weeks. Time to delivery was considered as time from the first day of admission to hospital until delivery. Maternal indications for delivery included HELLP syndrome, eclampsia, severe preeclampsia and worsening maternal status such as hypertension unresponsive to medical treatment, blurred vision, epigastric or right upper quadrant pain and oliguria. The only fetal indication for delivery was fetal distress shown by either biophysical profile or Doppler studies. Risk factors for preeclampsia included a history of hypertension; either chronic hypertension or a preeclampsia in previous pregnancy and history of diabetes, gestational or pre-gestational. Betametazone doses were considered as completed when delivery occurred after 24 hours of the last dose of betametazone.

Data were expressed as means ± standard deviation (SD) or percentages and analyzed with Student's t test, Chi-square test and correlations were made with Pearson correlation test. P<0.05 was considered statistically significant. SPSS for Windows (version 17.0; SPSS, Inc., Chicago, IL) was used for statistical analyses.

Results

Demographic characteristics and serum markers of the groups in the first trimester are presented in table 1. The patients in group II were significantly younger (30.6±6.27 vs. 27.9±6.25) (p=0.01). Data regarding admission and delivery are shown in table 2. Gestational week at delivery was significantly earlier for group II (33.6±3.9 vs. 32±3.3) (p=0.02). Maternal morbidity, mortality and intensive care unit (ICU) stay were similar (table 3). Group I patients had significantly more risk factors (16.9 vs. 2.3%) (p= 0.015). History of hypertension was also more common in group I (11 vs. 0%) (p= 0.023) (table 4). Fifty-two of 118 patients in group I and 17 of 43 patients in group II had data about the neonatal intensive care unit (NICU) stay. The IUGR frequency and neonatal morbidity and mortality of the groups were similar (table 5).

Table 1: Demographic characteristics and first trimester serum markers of the patients

	Group I (n=118)	**Group II (n=43)**	**p**
Age (years)(mean±SD)	30.6±6.27	27.9±6.25	0.01*
Nulliparity (%)	45.8%	55.8%	NS
BMI (mean±SD)	27.8±6.39	28±9.9	NS
Weight gain (mean±SD)	13.2 ±7.6	7.6±4.7	NS
f β-hCG (mean±SD)	1.21±0.98	1.02±0.59	NS
PAPP-A (mean±SD)	0.6±0.26	1.04±0.81	NS

**Statistically significant, NS: No significance, BMI: Body mass index F β-hCG: free beta human chorionic gonadotropin, PAPP-A: Pregnancy associated plasma protein- A*

Table 2: Data regarding the admission and delivery

	Group I (n=118)	**Group II (n=43)**	p
Gestational age at admission (weeks) (mean±SD)	32.9±4,2	31.6±3.2	NS
Time to delivery(days) (mean±SD)	4.5±10.5	2.5±6.3	NS
Gestational age at delivery (weeks) (mean±SD)	33.6±3.9	32±3.3	0.02*
Birth Weight (gram) (mean±SD)	1877±870	1549±528	NS
Delivery for maternal indications (%)	85.9	90.5	NS
Delivery for fetal indications (%)	14.1	9.5	NS

**Statistically significant*

Table 3: Data about maternal mortality and morbidity

	Group I (n=118)	**Group II (n=43)**	**p**
Plasental abruption (%)	1.7	0	NS
ICU stay (%)	9.3	16.3	NS
Stay in ICU(days) (mean±SD)	2.15±1.82	2.83±1.17	NS
Maternal mortality (%)	0.8	2.3	NS

Table 4: Data regarding the NICU stay and perinatal morbidity

	Group I (n=29)	Group II (n=11)	p
NICU admission	55.9%	62.8%	NS
Mean stay in NICU(days)	22.5±2.12	22± 14.14	NS
RDS	56.7%	36.4%	NS
Sepsis	13.3%	27.3%	NS
NEC	10.3%	0	NS
ICH	24,1%	0	NS
Betametazone doses completed	66.7%	33.3%	NS
Neonatal mortality(%)	55.6	44.4	NS
IUGR	55.1%	62.8%	NS

**Statistically significant, NS: No significance, NICU: Neonatal intensive care unit, RDS: Respiratory distress syndrome, NEC: Necrotizing enterocolitis, ICH: Intracranial hemorrhage, IUGR: Intrauterine growth restriction*

Table 5: Data regarding risk factors

	Group I (n=118)	Group II (n=43)	p
Risk factors present(%)	16.9	2.3	0.015*
History of hypertension(%)	11	0	0.023*
History of diabetes (%)	7.6	2.3	NS

**Statistically significant*

Discussion

This study revealed that patients with proteinuria of ≥5 g/24hr were significantly younger than patients with proteinuria of <5 g/24 hr (p=0.01) (table 1). Nulliparous patients are known to have more severe preeclampsia when compared to those with recurrent or superimposed preeclampsia.[1] However, the nulliparity frequency was similar in both groups. In our study the women with less severe proteinuria (group I) had superimposed and recurrent preeclampsia more frequently, which is consistent with the results of a study by Chen.[5] Chen demonstrated that recurrent or superimposed preeclampsia tends to be less severe than the first preeclampsia and is also associated with less severe proteinuria.

None of the BMI, weight gain and serum markers were predictive of preeclampsia (Table 1). Although not statistically significant, during pregnancy patients in group II gained less weight (13.2 ±7.6 vs. 7.6±4.7) (p=0.07). During the first trimester, f β-hCG and PAPP-A levels were also indifferent.

Newman et al. reported that massive proteinuria appears to be a marker for early onset of the disease and progression to severe preeclampsia;[6] however, in our study both groups were admitted to hospital at the same gestational age (Table 2). Group II patients were followed up for a shorter time and gestational age at delivery was significantly earlier for group II patients (p=0.02). There was a negative weak but significant correlation between the amount of protein in urine and gestational age at delivery (p=0.011, r=-0,017) and birth weight (p=0.025, r=-0,177). The percentages of the patients who were delivered due to maternal and fetal indications were similar in both groups. The mean birth weight of the babies in group II was lower. However, when the birth weight was corrected for gestational age, it was similar in both groups.

Chan et al. reported that as proteinuria increases, so does the risk of adverse maternal and fetal outcomes. They determined that a protein/creatinine ratio greater than 900 mg/mmol (corresponding to 9g/24h) in patients younger than 35, and a protein/ creatinine ratio greater than 500mg/mmol (corresponding to 5g/24h) in patients older than 35 greatly increased the likelihood of adverse maternal outcomes.[7]

The placental abruption (1.7% vs. 0%) and maternal mortality rates (0.8 vs. 2.3%) were similar (Table 3).

Although more patients in group II needed ICU stay (9.3 vs. 16.3 %), this was not statistically significant. There was a positive, weak but significant correlation between the amount of protein in urine with the need for ICU stay (p=0.001, r=0,252). Mean days spent in ICU were also similar. Selo-Ojeme et al. reported that hypertensive disorders were the most common cause of admission to ICU in obstetric patients.[8]

Newman reported that the morbidity was higher in the babies of patients with massive proteinuria.[6] Because these babies are delivered earlier, increased morbidity appears to result from prematurity rather than the degree of proteinuria. Nevertheless, Schiff et al. found no differences in maternal and fetal outcomes between pregnancies with marked increases in proteinuria and those with modest or no increases.[9]

In this study 55.9 % of the patients in group I and 62.8% of the patients in group II needed NICU stay. Mean days spent in NICU were similar (Table 4). Betametazone doses were completed more frequently in group I than group II because the time to delivery was longer for group I. Despite this, respiratory distress syndrome (RDS) was more common in group I. Sepsis was more common in group II and necrotizing enterocolitis and intracranial hemorrhage were more common in group I. However, none of these findings were statistically significant. Neonatal mortality of both groups was similar. There were 9 neonatal deaths. Five of these were in group I and 4 were in group II.

In our study antenatally 55.1% of group I and 62.8% of group II had IUGR. Srinivas et al. reported that preeclamptic women have a 2.7 times increased odds of having a fetus with

IUGR compared with controls.[10] Mitani reported that the incidence of severe hypertension and critical maternal complications was significantly higher in women with preeclampsia accompanied by IUGR than in those with preeclampsia without IUGR.[11] In our study IUGR had a negative, weak, but significant correlation with gestational age at admission (p=0.004, r= -0.223) and delivery (p=0.004, r= -0.224). There was also a positive, weak, significant association between IUGR and admission to NICU (p=0.000, r= -0.276).

Nulliparity, having a history of preeclampsia, gestational diabetes, essential hypertension, working during pregnancy, advanced maternal age, multiple pregnancy, pre-pregnancy obesity are risk factors for preeclampsia.[12,13] In our study most of the patients had no recognizable risk factors. When risk factors were reviewed, there appeared to be four main risk factors. The most common risk factors were having a history of chronic hypertension, or recurrent preeclampsia and pre-gestational and gestational diabetes mellitus. The patients who had a history of chronic HT and recurrent preeclampsia and patients having pre-gestational and gestational hypertension were assembled in two groups. Group I patients had significantly more risk factors (p=0.015), particularly a history of chronic hypertension or preeclampsia (p=0.023) (table 5). In our study superimposed and recurrent preeclampsia were common in group I patients. Chan et al. also reported that recurrent preeclampsia tends to be less severe than preeclampsia and is associated with less proteinuria.[7]

Homer et al. divided patients into gestational hypertension, proteinuric preeclampsia and non-proteinuric preeclampsia groups. In all groups systolic blood pressure was ≥140 mmHg and diastolic blood pressure ≥90 mmHg, appearing after the 20th gestational week.[14] Non-proteinuric preeclampsia patients had cardiac or renal disease plus evidence of involvement of other organs such as renal insufficiency, liver disease, neurological problems, hematological disturbances or fetal growth retardation. They reported that women with proteinuric preeclampsia had a worse pregnancy outcome, in particular greater perinatal mortality, when compared to women with non-proteinuric preeclampsia. Women with clinical features of preeclampsia including organ involvement without proteinuria have a worse pregnancy outcome when compared to women with gestational hypertension. Therefore, absence of proteinuria in the presence of hypertension developing after the 20th gestational week is not always suggestive of gestational hypertension. Involvement of other organs should be carefully searched. Otherwise, fetal morbidity is increased.

Conclusion

The patients with proteinuria of ≥ 5 g/24 hr are younger, deliver at an earlier gestational age and have risk factors less frequently. Although massive proteinuria is not an indication for delivery in preeclampsia patients, during the follow up physicians should be careful because there is evidence that the maternal or perinatal mortality may be increased. It should also be remembered that proteinuria or hypertension may not appear in eclampsia and HELLP syndrome. Additional tests to determine involvement of other organs should be performed in the presence hypertension without proteinuria before assuming that it is gestational hypertension.

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Şiddetli Preeklampsi Vakalarında Proteinüri ile Maternal ve Fetal Sonuçların ilişkisi

AMAÇ: Proteinüri miktarının kötü gebelik sonuçları ile ilişkisini incelemek.

GEREÇ VE YÖNTEM: Aralık 2005 ile Aralık 2011 tarihleri arasında Başkent Üniversitesi Adana Araştırma ve Uygulama Hastanesi'nde 37. gebelik haftasından önce doğurtulan 129 şiddetli preeklampsi, 11 eklampsi ve 21 HELLP sendromu vakasının sonuçları retrospektif olarak incelendi. Grup I'deki (n=118) hastaların 5 g/24 saatten az, grup II'deki hastaların ise 5 g/24 saate eşit veya daha fazla proteinürisi vardı. Verilen Student T test ve Ki- kare testi ile analiz edildi ve korelasyonlar Pearson korelasyon testi ile yapıldı. P>0,05 istatistiksel olarak anlamlı kabul edildi. SPSS (versiyon 17,0; SPSS, Inc., Chicago, IL) istatistiksel analiz için kullanıldı.

BULGULAR: Grup II'deki hastalar istatistiksel anlamlı olarak daha gençti (30,6±6,27 vs. 27,9±6,25) (p=0,01) ve daha erken doğum yaptı (33,6±3,9 vs. 32±3,3) (p=0,02). Grup I'deki hastaların daha fazla risk faktörleri vardı (16,9 vs. 2,3%) (p= 0.015). Hipertansiyon öyküsü Grup I' deki hastalarda daha sıktı (11 vs. 0%) (p= 0,023).

SONUÇ: Proteinürisi ≥5 g/24 saat olan kadınlar daha gençti, daha erken doğum yaptı ve daha nadiren risk faktörleri vardı.

Anahtar Kelimler: Proteinüri, Preeklampsi, Doğum

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