

Assessment of maternal and perinatal outcomes in pregnant women with isolated proteinuria

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Abstract

Objective: In the study, we aimed to identify the relationship between maternal and perinatal outcomes of pregnant women found to have isolated proteinuria, rates for progress towards preeclampsia and risk factors.

Methods: A total of 57 pregnant women who were at 24–34 weeks of gestation and admitted to our hospital for routine antenatal follow-up between December 2013 and December 2014 were included in our study. The patients with proteinuria but without elevated blood pressure were called as isolated gestational proteinuria (IGP) group. The patients were found to have new-onset elevated blood pressure during their antenatal follow-ups and the patients developing preeclampsia were defined as proteinuric pre-eclampsia (P-PE) group.

Results: Preeclampsia developed in the advanced weeks of gestation in 15 (26%) of 57 pregnant women. There was no significant difference between the body mass index values of both groups before pregnancy ($p>0.05$). While no significant difference between proteinuria amount and onset week of proteinuria was observed in both groups, there was a positive correlation in P-PE group between onset week of proteinuria and development week of preeclampsia. It was found that preeclampsia developed in most of the patients in this group within about 3 weeks after proteinuria developed. The neonatal outcomes of both groups were compared. While no significant difference was observed between birth weight, need for newborn intensive care unit and hospitalization period, mean week of delivery was significantly shorter in P-PE group ($p<0.005$). The complications of severe preeclampsia were not observed in IGP group.

Conclusion: Although proteinuria is usually a late sign of preeclampsia, it may sometimes develop before other signs. Close antenatal follow-up is very significant in the management of pregnant women found to have isolated proteinuria and it should be kept in mind that such patients may develop preeclampsia during further weeks of gestation. In our study, we found that isolated proteinuria in pregnant women is similar with proteinuric pre-eclampsia in particular in terms of both risk factors and perinatal outcomes.

Keywords: Isolated proteinuria, preeclampsia, maternal, perinatal outcomes.

Özet: İzole proteinürlü gebelerde maternal ve perinatal sonuçların değerlendirilmesi

Amaç: Çalışmada, izole proteinüri saptanan gebelerin maternal ve perinatal sonuçları, preeklampsiye ilerleme oranları, risk faktörleri arasındaki ilişkinin saptanması amaçlanmıştır.

Yöntem: Çalışmaya, Aralık 2013 – Aralık 2014 yılları arasında hastanemize rutin antenatal takip amacıyla başvurmuş olan, 24–34 gebelik haftasındaki, çalışma kriterlerine uygun 57 gebe dahil edildi. Proteinüri olup kan basıncı yüksekliği olmayan hastalar izole gestasyonel proteinüri (İGP) grubu olarak adlandırıldı. Hastaların antenatal takiplerinde yeni başlangıçlı kan basıncı yüksekliği olup preeklampsi gelişen grup ise proteinüri başlangıçlı preeklampsi (P-PE) grubu olarak tanımlandı.

Bulgular: Toplam 57 gebe kadının 15'inde (%26) ilerleyen gebelik haftalarında preeklampsi gelişti. İki grupta gebelik öncesi beden kitle indeksi değerleri arasında anlamlı farklılık saptanmadı ($p>0.05$). Proteinüri miktarı ve proteinüri başlangıç haftası arasında her iki grupta anlamlı farklılık saptanmazken, P-PE grubunda proteinüri başlangıç haftası ve preeklampsi gelişme haftası arasında pozitif korelasyon izlendi. Bu grupta proteinüri başladıktan sonra hastaların çoğunda ortalama 3 hafta içinde preeklampsi geliştiği saptandı. İki grup arasında neonatal sonuçlar karşılaştırıldı. Doğum kilosu, yenidoğan yoğun bakım ünitesi gereksinimi ve kalış süresi arasında anlamlı fark saptanmazken, ortalama doğum haftası P-PE grubunda anlamlı olarak daha kısa saptandı ($p<0.005$). İGP grubunda şiddetli preeklampsinin komplikasyonlarına rastlanmadı.

Sonuç: Proteinüri genellikle preeklampsinin geç bir bulgusu olmasına rağmen bazen diğer belirtilerden önce görülebilir. İzole proteinüri saptanan gebelerin yönetiminde yakın antenatal takip çok önemlidir ve bu hastaların ilerleyen gebelik haftalarında preeklampsiye ilerleyebileceği akıld tutulmalıdır. Bizim yaptığımız çalışma da gebelerdeki izole proteinürinin özellikle proteinüri başlangıçlı preeklampsi ile hem risk faktörleri hem de perinatal sonuçlar açısından benzer olduğunu göstermiştir.

Anahtar sözcükler: İzole proteinüri, preeklampsi, maternal, perinatal sonuçlar.

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Introduction

Preeclampsia (PE) is a multisystemic syndrome associated with increased maternal and perinatal morbidity and mortality affecting cardiovascular, hepatic and renal systems.^[1–4] It is estimated that its prevalence is approximately 4.6% (2.7–8.2%) worldwide.^[5] 10–15% of maternal deaths from obstetric complications are associated with preeclampsia/eclampsia.^[1]

Preeclampsia is the condition defined as the comorbidity of proteinuria or damage of target organ with new-onset hypertension after 20 weeks of gestation in a woman with the history of normotension. The severity of proteinuria is not proportional to the severity of PE. Therefore, the amount of proteinuria should not be considered as a guide in PE management.^[6–8] Proteinuria does not exist in 10% of women with clinical finding and no significant amount of proteinuria was found in the urine of 20% of women, who were established with eclampsia diagnosis, during the week before seizure.^[9,10] Proteinuria amount increases at third trimester independent from PE diagnosis. Dipstick urinalysis has low sensitivity (varying from 22% up to 86%) to determine significant amount of proteinuria in particular. 24-hour urinalysis in pregnant women found to have 1+ and more proteinuria by dipstick test is a golden standard to determine proteinuria amount.

Although proteinuria is usually a late clinical sign of preeclampsia, it may develop in some women without blood pressure elevation and this is called as isolated gestational proteinuria (IGP). It is unknown if IGP is a part of preeclampsia's disease spectrum. Soluble FMS-like tyrosine kinase 1 (s Flt-1) and soluble endoglin levels which are the classical biological markers of PE increases at medium level (between normal pregnancy and PE) in pregnant women with isolated proteinuria.^[11,12] The clinical studies investigating the progress of isolated proteinuria towards PE in pregnant women are limited. However, some clinical studies showed that some of the pregnant women diagnosed with eclampsia only had proteinuria finding during the week before first convulsion.^[13,14] Some clinical studies assert that isolated proteinuria in pregnant women is a type of mild PE.

The relationship of isolated gestational proteinuria with PE is not fully known. Therefore, in this study, we aimed to investigate the rate of progress towards PE in pregnant women with IGP, to compare maternal and perinatal outcomes in groups who developed and not developed PE and to reveal the relationship among risk factors in both groups.

Methods

We included 57 pregnant women in this retrospective study at their 24–34 weeks of gestation who admitted to the follow-up clinic of our hospital between December 2013 and December 2014 for routine antenatal follow-up. Those with previous history of renal and autoimmune diseases, pregnant women with chronic hypertension (HT), pregestational diabetes mellitus and urinary system infection and intrauterine fetal death, and multiple pregnancies were excluded from the study. The approval of local ethic committee of Zeynep Kamil Hospital was obtained for the study.

For routine antenatal follow-up, blood pressure measurement, full urinalysis and body weight measurement were performed. Systolic blood pressure (BP) being 140 mmHg and above and/or diastolic BP being 90 mmHg and above was defined as HT. Patients who were found to have 1+ and more protein without erythrocyte and leucocyte in the spot urine sample collected randomly, not found any proteinuria finding in previous urinalyses and who were normotensive (systolic BP <140 mmHg and diastolic BP <90 mmHg) were asked to collect 24-hour urine sample. Presence of protein more than 300 mg/day but lack of elevated BP in 24-hour urine was defined as isolated gestational proteinuria (IGP). These patients who had new-onset elevated BP during their regular antenatal follow-ups and developed PE were determined as P-PE (proteinuric pre-eclampsia) group. Both patient groups (IGP and P-PE) were called for polyclinic visit at least once a week after proteinuria was detected, and full blood count and routine biochemistry analysis were done during each antenatal examination. On this basis, the week that proteinuria started and additionally the week that BP elevated in the group developed PE was recorded.

Statistical method

The lowest and highest values of mean, standard deviation and median, and frequency and rates were used in the descriptive statistics of the data. The distribution of variables was measured by Kolmogorov Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative data. Chi-square test was used in the analysis of qualitative data; when chi-square could not meet the conditions, Fisher's test was used. Spearman correlation analysis was used for correlation analysis. The results were analyzed by SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Mean onset-week of proteinuria in both groups, PE development week in Group 1 and the comparison of protein levels in 24-hour urine.*

	Group 1		Group 2		p
	Mean/SD	Min/Max	Mean/SD	Min/Max	Mean
24-hour urine (g)	2520±3777	324–12.000	1151±1188	400–5400	0.273
Proteinuria week	29.1±3.3	24–33	28.2±2.8	24–34	0.332
Preeclampsia week	32.8±3.8	26–38			

*Independent sample t-test / Mann-Whitney U test / Chi-square test (Fisher's test)

Results

Hypertension was observed in advanced weeks of gestation in 26% (n=15) of a total of 57 pregnant women included in the study, and this group was assigned as P-PE group (Group 1). There was no elevated BP in remaining 42 (74%) patients, and this group was assigned as IGP group (Group 2). Maternal demographic characteristics of both patient groups included in the study were compared. Maternal mean age was 31.7±6.4 years in Group 1 and 28.8±5.4 years in Group 2. Body mass index (BMI) values calculated by the heights and weights of patients before pregnancy were over 26.1 kg/m², which is considered as a risk factor for PE, in both groups. No significant difference was observed in age, parity, PE history in previous pregnancy and smoking habit in both groups (p>0.05). Pregestational BMI value in Group 1 was significantly higher than Group 2 (p<0.05). Mean protein amounts in 24-hour urine of patients, mean onset week of proteinuria for both groups and the onset week of PE development in Group were shown in **Table 1**.

Onset week of proteinuria was found as 28.2±2.8 in IGP group and mean week of gestation for the onset of proteinuria was found as 29.1±3.3 in P-PE group (**Table 1**). Mean weeks of gestation for the onset of BP elevation was 32.8±3.8 (between the limits of 26 and 38 weeks) in Group 1. Also, it was found that PE developed after averagely 3.7 weeks following the development of proteinuria in this group. A relation between the onset week of proteinuria and the week that PE developed was shown in this group.

There was mildly positive correlation between onset week of proteinuria and preeclampsia week (p=0.033, r=0.552). In the laboratory tests of the patients, AST, ALT, LDH, uric acid, creatinine and thrombocyte values of both groups were compared but no significant difference was observed between two groups for thrombo-

Table 2. Comparison of laboratory values.

	Group 1	Group 2	p
	Mean±SD	Mean±SD	
Thrombocyte (/L)	229.6±45.1	246.7±82.4	0.814
Creatinine (mg/dl)	0.5±0.2	0.6±0.2	0.674
AST (U/L)	39±60	27.8±41.1	0.549
ALT (U/L)	34.1±50.5	26.9±48.2	0.892
LDH (U/L)	255.6±78.5	233.3±57.4	0.248
Uric acid (mg/dl)	5.9±1.3	5.2±1.5	0.126

cyte, creatinine, AST, ALT, LDH and uric acid (p>0.05) (**Table 2**).

The relationship between proteinuria amount in 24-hour urine and laboratory values was evaluated in both patient groups (**Table 3**). There was no correlation between 24-hour urine amount and thrombocyte, creatinine, AST, ALT values (p>0.05). Maternal complications and their outcomes were analyzed, but no maternal mortality was found in both groups. Severe PE findings such as pulmonary edema, renal failure (serum creatinine >1.2), eclampsia and neurological findings were not observed in both patient groups. Both groups did not have any need for adult intense care unit. Emergency delivery was decided due to the exacerbation of hypertension (systolic BP ≥170 mmHg and diastolic BP ≥110 mmHg) in 13% (n=2) of 15 patients and the development of HELLP syndrome in 20% (n=3) of 15 patients in Group 1.

Table 3. Relationship between proteinuria level in 24-hour urine and laboratory values.*

	Thrombocyte	Creatinine	AST	ALT
r	-0.006	0.065	0.034	0.241
p	0.963	0.633	0.800	0.071

*Spearman correlation analysis

No significant difference was found between Group 1 and 2 in terms of the distribution of delivery type; however, it was seen that the rate of cesarean section was higher than the rate of normal delivery in both groups. Mean birth weight did not show any significant difference between two groups ($p>0.05$). Those with birth weight below 2500g were 67% ($n=10$) of Group 1 while they were 57% ($n=24$) of Group 2. Mean delivery week was found to be 34.6 ± 3.1 weeks in Group 1 and 36.5 ± 2.8 weeks in Group 2, and the delivery week in Group 1 was significantly lower than Group 2 ($p<0.05$). While 9 (60%) of 15 patients in Group 1 had premature delivery before 37 weeks, 20 (48%) of 42 patients in Group 2 had premature delivery before 37 weeks. 1-minute and 5-minute Apgar scores in Group 1 & 2, the rate of newborns with 5-minute Apgar score below 7, and perinatal mortality rate did not show any significant difference ($p>0.05$) (**Table 4**).

There was no significant difference between RDS rates and mechanical ventilator need during hospital-

ization in neonatal intense care unit. Intraventricular bleeding, necrotizing enterocolitis and sepsis were not seen in both groups. Early/late neonatal mortality was also not seen in both groups, but intrauterine fetal death was observed only in 1 fetus in Group 1 during the follow-up. There was no significant correlation between the onset week of proteinuria and delivery week ($rs=-0.010$; $p=0.939$).

Discussion

In 2013, American College of Obstetrics and Gynecology (ACOG) defined new criteria for preeclampsia diagnosis and removed proteinuria from the essential criteria for PE. The presence of severe proteinuria (5 g/day) was also not included to severe PE criteria. Yet, most of women with PE are diagnosed with the presence of proteinuria. Therefore, screening for proteinuria during pregnancy is important. In a healthy woman who did not have any known disease

Table 4. Comparison of neonatal results.*

		Group 1		Group 2		p
		n	%	n	%	
Delivery	CS	13	87	30	71	0.249
	NSD	2	13	12	29	
Sex	Male	10	67	24	57	0.524
	Female	5	33	18	43	
Fetus weight (g)		2395 $\pm$ 1068		2557 $\pm$ 963		0.544
Week		34.6 $\pm$ 3.1		36.5 $\pm$ 2.8		0.043
NICU	Available	7	47	15	36	0.454
	N/A	8	53	27	64	
Period (week)		30.7 $\pm$ 20.8		33.0 $\pm$ 28.7		0.921
MV	Available	5	33	10	24	0.823
	N/A	2	13	5	12	
RDS	Available	3	20	5	12	0.674
	N/A	4	27	10	24	
Phototherapy	Available	6	40	7	17	0.083
	N/A	1	7	8	19	
Apgar 1		5.9 $\pm$ 2.7		6.8 $\pm$ 2		0.364
Apgar 5		7.4 $\pm$ 2.5		8.2 $\pm$ 1.7		0.249
5-minute <7	Available	9	60	33	79	0.161
	N/A	6	40	9	21	
Mortality	Available	1	7	0	0	0.268
	N/A	14	93	42	100	

*Mann-Whitney U test / Chi-square test (Fisher's test). CS: Cesarean, MV: Mechanical ventilator, NICU: Neonatal intense care unit, NSD: Normal spontaneous delivery, RDS: Respiratory distress syndrome

previously, the pathogenesis of isolated proteinuria started after 20 weeks of gestation could not be fully clarified. It is controversial that if isolated proteinuria in pregnant women is a part of PE disease spectrum or the result of physiological renal changes during pregnancy. It is known that proteinuria exacerbated during pregnancy associated with a known renal disease is related with increased poor obstetric outcomes. Yet, obstetric outcomes of isolated gestational proteinuria are not known well. Today, there is no prospective study defining the risk of progress towards PE in further weeks of gestation in pregnant women with isolated proteinuria and the current retrospective studies are limited.

This was first added into the literature in 2008 and Morikawa et al. found that HT developed in further weeks of gestation in 19 (51%) of 37 women who developed proteinuria in the absence of hypertension.^[15] Mean onset week of proteinuria in these 37 patients was found as 32.8 ± 4.8 weeks, HT developed at a mean week of 33 ± 4.7 in 19 (51%) of them and they were diagnosed P-PE. Onset weeks of proteinuria and PE weeks of pregnant women diagnosed with isolated proteinuria were found to be associated. The mean period between proteinuria and PE development in P-PE group is 2.1 ± 1.7 weeks. However, no significant difference was found between the onset week of proteinuria and the period up to delivery. In P-PE group, mean weeks of gestation were found as 35.1 ± 4.1 weeks, and 57.9% of them had premature delivery before 37 weeks of gestation while 26.3% of them had premature delivery before 33 weeks of gestation. Mean weeks of gestation in IGP group was found as 38.3 ± 1.4 weeks.^[15]

In the case-controlled study of Holston et al. in 2009 investigating obstetric outcomes of gestational proteinuria and the changes of angiogenic factors in serum, they found that poor obstetric outcomes are rare and angiogenic factor levels in serum are similar with PE, and they supported the hypothesis that IGP is a variant of mild PE.^[11]

Macdonald-Wallis et al. found in their study that the risk factors defined for PE are associated with proteinuria developing during normal term pregnancy.^[16] In their studies performed on 11,651 cases, they found an increased relationship between any type of proteinuria during pregnancy and the presence of increased pregestational BMI, young age, nulliparity and twin pregnancy. They revealed that there is a negative rela-

tionship between smoking and proteinuria. As a result, they identified that the PE risk factors defined were associated with the development of proteinuria in healthy term pregnant women, and they supported the hypothesis that IGP may be an early finding of PE.

In 2011, Yamada et al. published two case reports and stated that isolated gestational proteinuria may be the initial sign of severe PE.^[17] They remarked that one of two cases, who were normotensive and had protein amount more than 300 mg/day in 24-hour urine, developed ablatio placentae and other patient developed posterior reversible encephalopathy, and they stated that isolated gestational proteinuria might be associated with poor outcomes as a result.^[17]

The last study in the literature performed on this matter was published in 2015. In their retrospective cohort study, Shinar et al. found that PE developed in 21% (n=21) of a total of 99 women who were established with proteinuria diagnosis in a 5-year period between 2009 and 2014. They highlighted that pregnant women with IGH who are particularly primara and have high level of proteinuria had increased risk for PE and therefore they should be followed up closely until postpartum period.

In our study, PE developed in further weeks of gestation in 26% (n=15) of 57 pregnant women with isolated proteinuria. This is a significant rate if it is considered that proteinuria is a late clinical finding of PE. PE may occur only with proteinuria in women with no symptom and BP elevation. In our study, we also found the onset week of proteinuria similar in both groups.

In this study, we aimed to determine if these risk factors are similar by comparing two groups in terms of the risk factors defined for preeclampsia. We included singleton pregnancies which had no known chronic disease previously. We compared two groups in terms of particular risk factors defined for PE such as age (45-year), parity, pregestational BMI and presence of PE history in previous pregnancy. Although there was a significant difference between pregestational BMI values of two groups, we saw that BMI values of both groups were above 26.1 as in the risk factors defined for PE. We found no significant difference between two groups in terms of maternal age, preeclampsia history in previous pregnancy, smoking and parity. Unlike PE risk factors, we found that the rate of multipara patients who had no PE history in previous pregnan-

cies was higher. Also, the rate of non-smokers in both groups was higher.

We found positive correlation between the onset week of proteinuria and the development week of P-PE. PE developed in 73% of the women within 3 weeks at the latest after proteinuria developed. The sooner proteinuria starts, the earlier will PE develop during early weeks of pregnancy. The rate of fetus with low birth weight in early-onset PE is higher than the one in late-onset PE.^[18] Also, we found that early-onset PE is associated with higher fetal death, perinatal death and severe neonatal morbidity.^[19,20] In pregnancies with isolated proteinuria, it may be useful to increase the frequency of antenatal follow-up even if there is no elevated BP. Similar to the study of Yamada et al., we did not find any positive correlation between the onset week of proteinuria and delivery week. Similar to the same study, we found delivery week of Group 1 significantly lower than Group 2 ($p < 0.05$).^[17] The earlier mean delivery week finding in Group 1 may indicate that emergency preterm labor will be required by the exacerbation of P-PE. In pregnant women found to have isolated proteinuria, identifying whether it will progress towards P-PE or stay the same is significant for the management of these patients. In addition, absence of severe PE signs in pregnant women with IGP may indicate that isolated proteinuria may be a variant of mild PE and the management may be similar with those in mild PE.

Conclusion

Preeclampsia is a gestational complication associated with increased maternal and perinatal morbidity and mortality and it may be diagnosed only with the presence of isolated proteinuria without hypertension. It is useful to carry out antenatal follow-ups regularly and with frequent intervals for pregnant women found to have IGP during early weeks of gestation as PE may develop and cause preterm labors in the following weeks in some of these women. In our study, we found that isolated proteinuria in pregnant women is similar with proteinuric pre-eclampsia in particular in terms of both risk factors and perinatal outcomes. Studies with higher numbers of cases are needed to confirm our findings and to develop new follow-up and treatment methods.

Conflicts of Interest: No conflicts declared.

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