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RESEARCH ARTICLE

The Relationship of Cases with Isolated Proteinuria in Pregnancy with Maternal and Perinatal Outcomes

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Abstract

Introductıon: There are a limited number of studies in the literature on the obstetric consequences of isolated gestational proteinuria (IGP) disease and the progression of preeclampsia (PE). It has been stated that gestational proteinuria may be a risk factor for PE. With this study, we aimed to determine the risk factors for the development of PE in cases with isolated proteinuria during pregnancy and to compare the maternal and perinatal outcomes of the cases.

Methods: The study was designed as a retrospective cross-sectional study. Pregnant women over the 20th gestational week and diagnosed with proteinuria by 24 hour urine analysis were included in the study. Patients who were diagnosed with gestational proteinuria and did not develop PE during their follow up were classified as IGP and patients who developed PE.

Results: The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Week of gestation at delivery(p<.001)and the time between proteinurine detection and delivery(p=.002) were significantly lower in the PE group. In 52 of 185 patients with gestational proteinuria in total, proteinuria was detected an average of 32w 5d, and increased blood pressure and development of PE occured at an average of 35 weeks of gestation. NB intensive care requirement, preterm delivery and IUGR rates were found to be significantly higher in the group with PE. Ceserean delivery rate in IGP was calculated as 54.14%,ceserean delivery rate in PE was 78.85%. A significant correlation was found between the history of preeclampsia in the development of preeclampsia in IGP patients(OR: 11,000 (1,199-100,883), p=0.034) and increased urine proteinuria(OR: 1,0001 (1,000-1,001),p=0.007).

Conclusion: Patients who have had preeclampsia before and who have a high 24 hour urine value are more likely to return to PE. IGP has a more benign prognosis in terms of maternal and fetal compared to PE.

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Introduction

Preeclampsia (PE) is defined as hypertension that starts after the 20th gestational week in a pregnant woman with a normal blood pressure before, and proteinuria or multiple organ damage accompanying it. PE is a multi-systemic disease that affects the cardiovascular, hepatic and renal systems and is associated with increased maternal and perinatal morbidity and mortality.[1-4] The prevalence of PE has been found to be 2.7–8.2% worldwide.[5] Approximately 10--15% of maternal deaths due to obstetric complications have been shown to be associated with PE.[2]

Proteinuria is a pathological condition frequently observed in PE disease and indicates endothelial damage in glomerular tissue.[6] In a normal pregnancy, urinary protein excretion increases as the gestational week progresses and is accepted as a physiological change up to a certain level. However, with dipsticks +1 and above proteinuria (30 mg / dL), protein / creatinine ratio (PCR) 0.3 mg protein / mg creatinine or higher in spot urine sample, or presence of 300 mg / day and above protein in 24-hour urine sample It is considered pathological for all gestational weeks.[7, 8] Although proteinuria is still used in the diagnosis of PE, it has ceased to be an indispensable criterion in diagnosis, and no relationship has been shown between the amount of proteinuria and the severity of PE.[9] In addition, isolated gestational proteinuria (IGP) without PE is observed in some of the cases, starting from the 20th gestational week and returning to normal within the postpartum twelve weeks.[10] It is observed that it is clear whether IGP is a part of the disease spectrum and that PE may develop at varying rates of 33-51% in cases with IGP in studies. In addition, perinatal results of pregnant women with IGP were found to be similar to healthy pregnant women.[10] In biochemical studies, it was found that placental growth factor (PIGF) and soluble-FMS-like tyrosine kinase 1 levels (sFlt-1) in pregnant women with IGP were lower than preeclamptic pregnant women and higher than healthy pregnant women.[11] There are a limited number of studies in the literature on obstetric results of IGP and PE progression.[12,13] However, some authors state that gestational proteinuria may be a risk factor for PE.[12]

With this study, we aimed to determine the risk factors for the development of PE in cases with isolated proteinuria during pregnancy and to compare the maternal and perinatal outcomes of the cases.

Material and Methods

The study was designed as a retrospective cross-sectional study. The data of pregnant patients whose follow-up and treatment was continuing between 2010-2019 in the Department of Obstetrics and Gynecology, Faculty of Medicine, Selcuk University, were analyzed. Approval was obtained from the local ethics committee of Selçuk University for the study (Reg. No=2019/257).

The pregnant women who were above the 20th gestational week and whose diagnosis of proteinuria were confirmed as a result of 24 hour urine analysis were included in the study. Patients with renal and autoimmune diseases, chronic hypertension, pre-gestational diabetes and urinary tract infection were not included in the study.

Patients who were diagnosed with gestational proteinuria and did not develop PE during their follow up were classified as IGP and those who developed as preeclampsia. Demographic and laboratory factors between these two groups; age, gravida, parity, body mass index (BMI), urine dipstick result, spot urine P / K ratio, protein level in 24-hour urine, gestational week in which proteinuria was first detected, gestational week at which delivery takes place, and time between detection of proteinuria and the time of delivery, from perinatal and maternal consequences; maternal intensive care need, neonatal intensive care need, newborn birth weight, PPROM, preterm delivery, IUGR, C / S ratios and APGAR 1st and 5th minute scores were compared.

The diagnostic criteria for PE were determined according to the criteria defined by the American College of Obstetrics and Gynecology Association.[14]

Statistical Analysis

SPSS 21 (Statistical Package for Social Sciences) program was used for statistical analysis while evaluating the findings obtained in the study. Descriptive statistical methods (mean, standard deviation, frequency) were calculated while evaluating the study data. Student t test was used for comparing parameters showing normal distribution between two groups and Mann Whitney U test was used for comparing parameters that did not show normal distribution between two groups. The Chi-Square test was used to compare qualitative data. Univariate and multivariate binary logistic regression analysis were used to predict preeclampsia. Results were evaluated at 95% confidence interval and significance level of $p < 0.05$.

Results

Records of 66604 pregnant patients were reviewed. It was found that 1808 pregnant women were followed up and treated with dipstick method, 1011 pregnant women with PCR and 206 pregnant women with a pre-diagnosis of proteinuria in 24-hour urine. 21 of the 206 patients were excluded from the study because of additional systemic diseases. The frequency of gestational proteinuria in the study was found to be 0.28% (185/66604). PE development was observed in 52 (28.11%) of 185 pregnant women with gestational proteinuria included in the study. The mean age of the patients included in the study was calculated as 28.69 ± 5.68 years. The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Accordingly, between the two groups; while there was no significant difference in terms of age, gravida, parity, BMI and first week of gestation in which proteinuria was detected ($p<.05$); dipstick urine result ($p<.001$), spot urine PCR ($p = .046$) and 24 hour urine protein values ($p = .001$) were found to be significantly higher in the PE group. Week of gestation at delivery ($p<.001$) and the time between proteinurine detection and delivery ($p = .002$) were significantly lower in the PE group (Table 1).

Table 1. Comparison of demographic data of the groups

	Isolated proteinuria (n=133)	Preeclampsia (n=52)	p-Value
Age	28,20 ± 5,40	29,94 ± 6,24	0,061
Gravida	2,18 ± 1,35 (1-7)	2,50 ± 1,48 (1-7)	0,149
Parite	0,94 ± 1,09 (0-6)	1,12 ± 1,22 (0-6)	0,452
BMI (kg/m²)	32,51 ± 3,71	33,00 ± 4,30	0,446
The result of dipstick	1,19 ± 0,8	1,33 ± 0,94	**< 0,001**
Protein/kreatinin (mg/g)	0,61 ± 0,67	0,96 ± 1,08	**0,046**
Proteinuria in urine for 24 hours (mg/day)	691,78 ± 909,63	1431,48 ± 2071,75	**0,001**
The first detection of gestational week	33 (20-39)	33 (20-38)	0,668
Gestational week of birth	38 (26-41)	37 (20-39)	**< 0,001**
The time between the first detection and birth (day)	38,96 ± 35,52	24,29 ± 30,49	**0,002**

Data were analyzed by independent sample t-test, Mann-Whitney U test, Pearson Chi-square.
Data were given as mean ± standard error, median (min-max) or as n (%)
BMI, body mass index.

In 52 of 185 patients with gestational proteinuria in total, proteinuria was detected at an average of 32w 5d, and increased blood pressure and development of PE occurred in the 35th gestational week. Birth took place when the average was 36w 1d. In the remaining 133 IGP patient group, the average week of proteinuria onset is 32w 2d, and the average week of gestation at birth is 37w5d (Figure 1).

Figure 1.

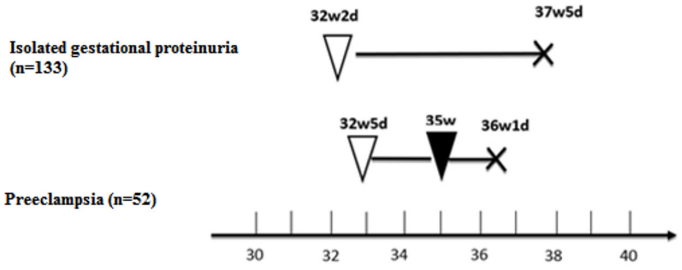

Figure 1. The development of PE with the occurrence of hypertension in the period from the time of detection of proteinuria to then birth.

Perinatal complications and fetal results of the patients are shown in Table 2. While there was no significant difference between the two groups in terms of PPROM development and the baby's first and fifth minute Apgar scores at birth, maternal intensive care requirement, NIC intensive care need, preterm delivery and IUGR rates were found to be significantly higher in the group with PE. In parallel with this result, HF birth weight was found to be significantly lower in the group with PE.

Table 2. Comparison of between perinatal complications and fetal deciency groups

	Isolated proteinuria (n=133)	Preeclampsia (n=52)	P-value
Mother intensive care (n,%)	1 (%0,75)	2 (%3,85)	**< 0,001**
PPROM (n,%)	2 (%1,5)	1 (%1,92)	0,749
Preterm birth (n,%)	19 (%14,29)	26 (%50,00)	**< 0,001**
Neonatal intensive care (n,%)	15 (%11,28)	17 (%32,69)	**< 0,001**
IUGR (n,%)	10 (%7,52)	17 (%32,69)	**< 0,001**
APGAR 1	7 (5-9)	7 (5-9)	0,461
APGAR 5	9 (6-10)	9 (6-10)	0,915
Neonatal weight	3080,70 ± 627,78	2504,75 ± 734 ,00	**< 0,001**
Caesarean section rate (n,%)	72 (%54,14)	41 (%78,85)	**0,001**
Gender boy	68 (%51,1)	31 (%59,6)	0,298
girl	65 (%48,9)	21 (%40,4)	

Data were analyzed by independent sample t-test, Mann-Whitney U test, Pearson Chi-square. Data were given as mean ± standard error, median (min-max) or as n (%). BMI, body mass index. PPROM : Preterm prematür membran.

When the IGP and PE patient groups were compared in terms of delivery type, a statistically significant difference was observed, and the rate of cesarean delivery was found to be higher in the group with PE (Cesarean delivery rate in IGP is 54.14%. Cesarean delivery rate in PE is 78.85%). When a comparison was made in terms of newborn gender in both patient groups, it was observed that the rate of male babies was higher.(59.6% in the PE patient group, 51.1% in the IGP patient group).

Variables for the prediction of preeclampsia in patients with isolated gestational proteinuria were examined by univariate and multivariate regression analysis. In univariate analysis, it was shown that preeclampsia history (OR: 11,000 (1,199-100,883), p = 0.034) and increased proteinuria in 24-hour urine (OR: 1,001 (1,000-1,001), p = 0.007) were found to be independently significant in the development of preeclampsia in IGP patients. In the multivariate analysis, a history of preeclampsia (OR: 12.675 (1.374-116.948), p = 0.025) and increased proteinuria in 24-hour urine (OR: 1.00 (1,000-1.001), p = 0.005) were shown to be statistically significant (Table 3).

Table 3. Prediction of preeclampsia of isolated gestational proteinuria patients

	Preeclampsia			
	Univariate		Multivariate	
Parameters	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.056 (0,997-1,119)	0,063		
Gravida	1,173 (0,938-1,467)	0,163		
BMI	1,033 (0,951-1,122)	0,444		
Preeklampsia history (yes)	11,000(1,199-100,883)	**0,034**	12,675 (1,374-116,948)	**0,025**
The first week of diagnosis	1,025 (0,956-1,099)	0,485		
Proteinuria in 24 hour urine	1,001 (1,000-1,001)	**0,007**	1,001(1,000-1,001)	**0,005**
Multiple pregnancy (yes)	0,850 (0,086-8,359)	0,889		
Fetal sex (boy)	1,411 (0,737-2,703)	0,299		

Univariate and multivariate logistic regression analysis was performed. BMI, body mass index, CI, confidence interval; OR, odds ratio. Bold values refer to statistical significance ($p < .05$)

Discussion

In our study, data of 185 patients who received proteinuria with 24-hour urine analysis during pregnancy were analyzed. PE development was observed in 52 (28.11%) of these pregnant women. The frequency of gestational proteinuria in the study was found to be 0.28% (185/66604). The average time between the detection of proteinuria and the development of PE was calculated as 16 days. Maternal and fetal outcomes were worse in the PE group. High 24-hour urine output and a history of preeclampsia were also found to be independent risk factors in the transition to preeclampsia.

PE is a multisystemic syndrome that affects the cardiovascular, hepatic and renal systems, associated with increased maternal, perinatal morbidity and mortality.[1-4] Many risk factors associated with preeclampsia have been identified. Obesity, nulliparity, multiple pregnancy, maternal age of more than 35, a mother's history of preeclampsia in a previous pregnancy, hyperhomocystinemia, metabolic syndrome and pre-pregnancy diabetes mellitus increase the risk of developing preeclampsia.[15,16] The presence of a previous history of preeclampsia increases the risk of preeclampsia by 8 times compared to those who do not have such a history.[17,18] Despite many studies conducted, the pathophysiology of preeclampsia is still not clearly understood today. Many theories have been put forward to explain the cause of preeclampsia. What is considered important today:[19] 1)Placentation with abnormal trophoblastic invasion of uterine vessels. 2)Immunological tolerance deconformity between maternal, paternal(placental) and fetal tissues. 3)Systemic endothelial dysfunction. 4) Inflammation/Infection. 5)Genetic, nutritional and environmental factors.

A normal pregnancy causes many anatomical and physiological changes in the urinary system. During pregnancy, the kidney size grows by approximately 1 ~ 1.5 cm and an increase in weight is observed.[11] Renal plasma flow (RPF) begins to increase in the early weeks of pregnancy and this increase is shown as one of the causes of renal hyperfiltration. The glomerular filtration rate (GFR) also increases, as does RPF. This increase is 50% more at the end of the first trimester than in the pre-pregnancy period, and this condition persists until the end of pregnancy. Around in the third moon after giving birth returns to normal levels.[7] In the studies conducted, the mechanisms underlying the significant increase in RPF and GFR have been examined. It has been observed that relaxation is important in the increase of GFR and RPF during pregnancy.[8] Relaxin increases the production of endothelin and nitric oxide in the renal

circulation. As a result, it leads to a decrease in renal afferent and efferent arteriole resistance with renal vasodilation, thereby increasing renal blood flow and GFR.[19] Failure in this critical adaptation is associated with poor pregnancy outcomes such as preeclampsia and intrauterine growth retardation.[20] Protein secretion secondary to the physiological changes of pregnancy increases from the kidneys during pregnancy and is considered a normal finding up to a certain level. However, the presence of 300mg or more protein in a 24-hour urine sample is considered pathological for all gestational weeks.[8,19] Proteinuria indicates endothelial damage. Although proteinuria is not an indispensable criterion for the diagnosis of PE, screening for proteinuria still has an important place, since most of the pregnant women who develop PE in the clinic are diagnosed with the presence of proteinuria. Another debate on proteinuria is IGP, and there are limited data in current guidelines on the subject of diagnosis and treatment of hypertension in pregnancy.[20,21] IGP frequency and pathogenesis have not been clearly elucidated. In some studies on the presence of proteinuria in preeclampsia, vascular endothelial growth factor and increased soluble tyrosine kinase 1 levels are held responsible for the pathogenesis of proteinuria.[22-26] Studies on IGP also support these results. However, it should be noted that placental growth factor (PIGF) and soluble-FMS-like tyrosine kinase 1 levels in pregnant women with IGP were found to be lower than preeclamptic pregnant women and higher than healthy pregnant women.[11] In the light of this information, IGP, PE diagnosis should PE be positioned as a criterion within the spectrum of disease or whether PE could be an early form of the disease spectrum .

IGP frequency is not known exactly like its pathogenesis. There are two prospective studies in the literature that state it as 4%.[27,28] Ekiz et al. This rate was reported as 0.33%, while this rate was found to be 1.4% in a multi-center observational study.[22,29] In our study, the frequency of IGP was found to be 0.28% in our patient group, where 66604 patients were screened and 185 patients were included in the study over a 10-year period. It is known that the risk of developing PE increases in IGP cases. In our study, it was found that 28.11% (52/185) of pregnant women with IGP developed PE in the following weeks of gestation. Considering that proteinuria is a late clinical manifestation of preeclampsia and that it can sometimes occur without any symptoms or high blood pressure, this is an important rate. Erkenekli et al.[30] Found the rate of patients who progressed from IGP to Preeclampsia as 35%, while Ekiz et al. Similarly found this rate as 33.7%.[22] Yamada et al,[29] this rate was given as 25% in a multi-center study. Morikawa et al.[31] Showed in their study that isolated proteinuria developed in the second half of pregnancy, and that PE developed in 51% of the cases. These studies have shown that after the detection of IGP, the frequency of development of PE may vary depending on the variety of environmental factors exposed, the difference and number of patient groups included in the study, but it can be said that approximately 25% to 50% of these patients will develop PE.

The average time from the detection of isolated gestational proteinuria to the development of PE was found to be 16 days in our study. In another study on this subject, it was reported that this period ranged from 3 days to 20 days and was 10 days on average. [32]

In our study in which there were 185 IGP patients in total, blood pressure increased in an average of 35 weeks of gestation in 52 patients and PE developed. While the mean onset week of proteinuria in 52 patients with PE was 32w5d, the week of delivery was 36w1d. In the remaining 133 isolated proteinuria patients group, mean proteinuria detection week was 32w2d and the week of delivery was 37w5d. In the light of these findings, it was found that proteinuria occurred at the same time in the patient group with PE (n = 52) and in the isolated proteinuria patient group (n = 133), while it was found that delivery occurred earlier in the patient group with PE. In a study conducted by Akaishi et al. On this subject, it was shown that the onset of proteinuria and delivery were earlier in the group with PE.[28] Our study findings support the study of Akaishi et al. In terms of timing of delivery. Proteinuria first detection week was found to be similar in the PE patient group and the IGP patient group in our study. In addition, when the first detected dipstick urine result, spot urine protein / creatinine ratio and 24-hour urine proteinuria were examined in the IGP and PE patient groups, it was observed that each of them was high in the PE developing group, and the repeated 24-hour urine proteinuria measurements during pregnancy also tended to increase in the group developing PE.

Since the possibility of developing PE in pregnant women with IGP is high, it is extremely valuable to determine the risk factors that predict

PE development. However, there is not enough data about this in the sources. Macdonald-Wallis et al. In a study they conducted with 11,651 cases, they found that pre-gestational BMI, young age, twin pregnancy and nulliparity, among the defined risk factors for PE, were associated with proteinuria occurring in normal term pregnancy.[33] In our study, it was found that having a history of preeclampsia (OR: 11,000 (1,199-100,883), p = 0.034) and increased proteinuria in 24-hour urine (OR: 1,001 (1,000-1,001), p = 0.007) predicted the development of preeclampsia.

There are few studies comparing the perinatal outcomes of IGP patients with and without PE in IGP patients. Ekiz et al. in their study, in which they retrospectively scanned 31472 patients and included 157 cases with IGP, it was shown that the week of birth was earlier, birth weights were lower and the need for neonatal intensive care was higher in the group with PE.[22] Our study also supports these findings, and the rate of preterm delivery was found to be significantly higher in the group with PE (50.00% in PE cases). In IGP cases, the preterm delivery rate was found to be 14.29%, and it was similar to the general population rates . In addition, in the group diagnosed with PE, the neonatal birth weight is lower (average newborn weight of IGP is 3080.70 ± 627.78 g, while the average PE weight is 2504.75 ± 734.00 g). while 11.3%, PE neonatal intensive care need was 32.7%) and maternal intensive care need was higher. There was no significant difference between the two groups in terms of PPROM, newborn 1st and 5th minute Apgar scores, and the amount of proteinuria observed in the postpartum period.

In some studies examining the gender distribution of babies of mothers with PE, the rate of male babies is high, in line with our results, and the reason is not known exactly.[34,35] When the sex ratios of newborn babies with and without PE were examined, it was found that the rate of male babies was higher in both patient groups (male babies rate in IGP 51.1% and male babies in PE 59.6%). In addition, in the univariate regression analysis, although it was not statistically significant, it was found that having a male baby increased the risk of developing PE (OR: 1.411 (0.737-2.703), p = 0.299).

The limitation of the study is that it is a retrospective study and the number of patients is small. The advantage is that there are not many studies on this subject in the literature.

PE is a pregnancy complication associated with increased maternal and perinatal morbidity and mortality worldwide. Since only proteinuria can be detected in some preeclamptic patients at the beginning without developing hypertension, pregnant women with isolated proteinuria should be given consultancy on PE and antenatal follow-up should be done regularly and at frequent intervals. Because PE may develop between 25% and 50% of the patients in the following weeks of gestation, causing both maternal and perinatal unwanted pregnancy complications.

Although pregnancy outcomes of IGP cases have been reported as positive in most of the studies conducted on this subject, there is a considerable possibility of developing preeclampsia in these patients. Although we see that the perinatal outcomes of pregnant women with IGP do not deteriorate in our study, close follow-up of women with a history of PE and high proteinuria in their previous pregnancies is extremely important in terms of PE development.

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