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THE CHANGES OF RENAL FUNCTION STATUS BASED ON PROTEINURIA AND GLOMERULUS FILTRATION RATE IN PATIENTS WITH HISTORY OF PREECLAMPSIA WITH SEVERE FEATURES

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ABSTRACT

Background: Preeclampsia with severe features is an endothelial disease that causes renal system disorders during pregnancy. Preeclampsia is an important cause of acute kidney injury and risk for chronic kidney disease.

Methods: This study was a case series conducted at the Department of Obstetrics and Gynecology, H. Adam Malik General Hospital Medan, Indonesia starting from December 2019 until January 2020. Total sampling technique was employed obtaining 31 subjects with a history of preeclampsia with severe features for at least 3 months to 2 years postpartum, without a history of chronic disease, diabetes mellitus, and congenital kidney disorders. Proteinuria, serum creatinine, and GFR calculations were performed.

Results: There were 31 patients who met the inclusion and exclusion criteria. At a time interval of 4 - ≤13 months postpartum, levels of proteinuria +1 (0-2), serum creatinine 0.81 ± 0.21 mg/dl, and levels of GFR 109.57 ± 25.13 (ml/min/1.73 m^2). Whereas at the time interval of >13 - 24 months postpartum, levels of proteinuria +1 (0-3), serum creatinine 0.85 ± 0.23 mg/dl, and GFR levels of 104. 41 ± 28.45 (ml/min/1.73 m^2). The mean of serum creatinine before delivery was 0.69 ± 0.15 mg/dl and after delivery was 0.83 ± 0.22 mg/dl. The mean of GFR postpartum at group of history of early onset preeclampsia was 103.07 ± 25.23 (ml/min/1.73 m^2) and group of history of late onset preeclampsia was 113.40 ± 28.24 (ml/min/1.73 m^2).

Conclusion: There was a tendency for a decrease in renal function among women with a history of preeclampsia with severe features with findings of persistent proteinuria from more than 3 to 24 months postpartum, an increase in mean of serum creatinine levels from before and after delivery and a decrease in GFR, but it was not significant. This was related to the slow course of chronic kidney disease, so it had to be followed up periodically.

KEYWORDS : Glomerular filtration rate (GFR), Preeclampsia with severe features, Proteinuria, Serum creatinine.

1. INTRODUCTION

Based on the data from World Health Organization (WHO) in 2017, there were approximately 295,000 maternal deaths during and after pregnancy and at delivery. The Maternal Mortality Ratio (MMR) in low-income countries in 2017 was 462 per 100.000 live births compared to 11 per 100.000 live births in high-income countries. The main complications that cause almost 75% of all maternal deaths are bleeding, infection, hypertension during pregnancy (preeclampsia and eclampsia), complications of childbirth, and unsafe abortion [1].

Preeclampsia and eclampsia are one of the main causes of maternal morbidity and mortality in the world, especially in developing countries with incidence ranging from 0.3% to 0.7%, while in developed countries the incidence is lower, namely 0.05% up to 0.1% [2]. In Indonesia, based on the data of Inter-Censur Population Survey (SUPAS) 2015, the MMR was 305 per 100,000 live births. Preeclampsia and eclampsia ranked third as causes of maternal mortality, around 27.1% [3].

Preeclampsia results in changes to several organ systems, including kidneys. In general, preeclampsia disrupts renal function, both prerenal and renal. In the renal part, there are changes in the renal parenchyma, experiencing glomerular enlargement followed with swelling of endothelial cells and loss of glomerular endothelial fenestrae (glomerular capillary endotheliosis). In addition, there is vasoconstriction, which results in decreased blood flow to kidneys. This pathological condition causes Glomerular Filtration Rate (GFR) to decrease and excretion rate of creatinine and urea to also decrease, resulting in accumulation of creatinine and urea in the plasma [4, 5, 6]. Spasms of renal arteries that cause salt and water retention which in turn lead to impaired absorption of protein resulting in proteinuria [7].

Preeclampsia may be an important cause of acute kidney injury and an important risk marker for subsequent chronic kidney disease. Wu et al. showed that women with hypertensive disorders during pregnancy had higher risk for postpartum chronic renal failure than women with normal blood pressure during pregnancy [8]. Veronica et al. concluded that monitoring of renal function was relevant to about one in seven women with a history of preeclampsia, mainly due to proteinuria. The risk for kidney disease after

preeclampsia was also hypothesized to be a primary renal insult and associated with risk factors for cardiovascular disease [9]. Therefore, it is important to consider long-term renal function assessment. The things observed were proteinuria, serum creatinine and GFR [10].

Based on the above background, researchers are interested in doing research on how renal function status changes based on proteinuria and glomerular filtration rate in patients with history of preeclampsia with severe features.

2. MATERIALS AND METHOD

The design of this study was a *case series*. This study was conducted from December 2019 until January 2020. This study was approved by the Ethics Committee of Faculty of Medicine, University of Sumatera Utara. Samples were taken by total sampling technique from medical records of the Department of Obstetrics and Gynecology, H. Adam Malik General Hospital Medan, Indonesia with total 31 samples meeting the inclusion and exclusion criteria. Inclusion criteria were women with history of preeclampsia with severe features that had passed at least 3 months to 2 years postpartum. The exclusion criteria were women who had history of chronic hypertension before pregnancy, women with history of chronic kidney disease before becoming pregnant with preeclampsia, and women with history of diabetes mellitus, women with congenital renal abnormalities, women with history of hemodialysis before pregnancy with preeclampsia, women who were not pregnant within the defined study period (more than 3 months to 2 years postpartum). Home visit was carried out to all subjects who were to be subjected to anamnesis, physical examination (measurement of body weight, height, BMI, blood pressure), by taking 5 ml blood from the cubital median vein, and taking urine samples while using the midstream urine technique. The serum creatinine and proteinuria tests were conducted at Prodia Clinical Laboratory Medan. GFR calculations were performed using *Cockcroft and Gault* formula. Data were analyzed statistically using SPSS version 22.0.

3. RESULTS

Table 1. Characteristics of the study subjects.

Characteristics	All Subjects (n = 31)
Age (years old)	30.93 ± 5.35
Postpartum Interval (Months)	13 (4-24)
BMI (kg/m^2)	27.82 ± 2.13
Parity	
Primigravida	11 (35.5%)
SG (Nullipara)	1 (3.1%)
Secundigravida	4 (12.9%)
Multigravida	15 (48.42%)
Onset of preeclampsia	
Early onset (<34 weeks)	19 (61.3%)
Late onset (≥ 34 weeks)	12 (38.7%)
Prehypertension Hypertension *Stage* I	6 (19.35%) 19 (61.29%)
Hypertension *Stage* II	6 (19.35%)

Based on the characteristics of the 31 study subjects, the mean of age was 30.93 ± 5.35 years old. The postpartum interval, from delivery to the study, obtained mean of interval i.e. 13 months in which the shortest interval was 4 months and the longest interval was 24 months. The mean of Body Mass Index (BMI) in all study subjects was 27.82 ± 2.13 kg/m^2. Parity was divided into primigravida in 11 subjects (35.5%), secundigravida (Nullipara) in 1 subject (3.1%), secundig ravida in 4 subjects (12.9%), and multigravida in15 subjects (48.42%). The onset when diagnosis of preeclampsia with severe features was confirmed in the last pregnancy was divided into early onset in 19 subjects (61.3%) and late onset in 12 subjects (38.7%). Based on the hypertension classification of JNC VIII, there were 6 subjects (19,35%) in the prehypertension group, 19 subjects (61,29%) in the hypertension group *stage* I, and 6 subjects (19,35%) in the hypertension group *stage* II.

Table 2. The relationship of proteinuria, serum creatinine, and glomerular filtration rate (GFR) postpartum based on postpartum time intervals.

	Postpartum interval (months)		*p value*
	4- ≤13 months	> 13-24 months	
Proteinuria	1 (0-2)	1 (0-3)	0,267 **
Serum creatinine (mg/dl)	0,81 ± 0,21	0,85 ± 0,23	0,597 *
GFR (mL/min/1,73 m2)	109,57 ± 25,13	104,41 ± 28,45	0,596*

**T-Independent Test*
*** Mann-Whitney Test*

The mean of proteinuria levels at postpartum interval 4 - ≤13 months was +1 which lowest level was 0 and highest level was +2; and that of at postpartum interval > 13 - 24 months was +1 which lowest level was 0, th highest level was +3, and p value was 0.267. The mean of serum creatinine levels at the postpartum interval 4 - ≤13 months was 0.81 ± 0.21 mg/dl and that of at post partum interval >13 - 24 months was 0.85 ± 0.23 mg/dl, and p value 0.597. The mean of glomerular filtration rate (GFR) at postpartum interval 4 - ≤13 months was 109.57 ± 25.13 (ml/min/1.73 m^2) and that of at postpartum interval >13 to 24 months was 104.41 ± 28.45 (ml/min/1.73 m^2), and p value 0.596.

Table 3. The stages of kidney disease based on glomerular filtration rate (GFR)

Stage of Kidney Disease	n	Percentage (%)	GFR (ml/min/1,73 m^2)
Stage I (LFG: ≥90)	23	74.2	107.08 ± 22.86
Stage II (LFG: 60-89)	8	25.8	78.30 ± 9.2

Stage I of kidney disease was found in 23 subjects (74.2%) with mean of GFR 107.08 ± 22.86 (ml/min/1.73 m^2). Stage II of kidney disease was found in 8 subjects (25.8%) with mean of GFR 78.30 ± 9.2 (ml/min/1.73 m^2).

Table 4. The stage of kidney disease based on postpartum interval

Postpartum Interval (Months)	Stage I (GFR: ≥90)	Stage II (LFG: 60-89)	Total	*p value*
4- ≤13	12 (75%)	4 (25%)	16	> 0.05
> 13-24	11 (73.3%)	4 (26.7%)	15	
Total	23 (74.2%)	8 (25.8%)	31	

Fisher's Exact Test

Stage I of kidney disease at postpartum interval 4 - ≤13 months was found in 12 subjects (75%) and that of at postpartum interval >13 - 24 months was found in 11 subjects (73.3%). Stage II of kidney disease at postpartum interval 4 - ≤13 months was found in 4 subjects (25%) and that of at postpartum interval >13 - 24 months was found in 4 subjects (26.7%).

Table 5. The relationship between proteinuria and serum creatinine levels before delivery and after delivery

	Before delivery	After delivery	*p value*
Proteinuria	3 (1-3)	1 (0-3)	0,000
Serum creatinine (mg / dl)	0,69 ± 0,15	0,83 ± 0,22	0,009

Wilcoxon Test

The mean of proteinuria levels before delivery was +3 with the lowest levels was +1 and the highest levels was +3 and the

mean of proteinuria levels after delivery was +1 with the lowest levels of 0 and the highest levels was +3, p value was 0,000. The mean of serum creatinine levels before delivery was 0,69 ± 0,15 mg/dl and the mean of serum creatinine levels after delivery was 0,83 ± 0,22 mg/dl, p value was 0,009.

Table 6. The relationship of glomerular filtration rate postpartum based on onset of history of preeclampsia with severe features

	The onset of history of preeclampsia with severe features		*p value*
	Early Onset	*Late Onset*	
GFR (ml/min/ 1,73 m^2)	103,07 ± 25,23	113,40 ± 28,24	0,298

T-Independent Test

The mean of glomerular filtration rate postpartum in the group of history of early onset preeclampsia was 103.07 ± 25.23 ml/min/1.73 m^2 and that of in the group of history of late onset preeclampsia was 113.40 ± 28.24 ml/min/1.73 m^2, p value 0.298.

5. DISCUSSION

The mean of age for all subjects in this study was 30.93 ± 5.35 years old. This was relevant to the study of Ilhami et al. The mean age of preeclampsia patients in their study was 30.03 ± 6.81 years old [11]. Lai et al. also found that the mean age of preeclampsia patients was 31.58 ± 6.2 years old [12]. The prevalence of chronic kidney disease in adults was generally found at older age, whereas the prevalence of chronic kidney disease in women with history of preeclampsia was found at younger age and had 4 to 5 times higher risk for kidney failure compared to women without history of preeclampsia [13].

As to characteristics of the postpartum interval, from delivery to research, the mean was 13 months with the shortest interval of 4 months and the longest interval of 24 months. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines state that any indication of kidney disease that is persistent for more than 4 months is considered a chronic condition, regardless of the etiology. Meanwhile, the guidelines National Kidney Foundation (NKF) defines that chronic kidney disease is kidney damage for > 3 months with or without a decrease in glomerular filtration rate (GFR). Approximately 6% of women with a history of preeclampsia experience an increase in albumin to creatinine ratio (ACR) at 2 years postpartum [14].

The mean of body mass index (BMI) found was 27.,82 ± 2.13 kg/m^2. It was relevant to the study from Veronica et al. who found mean of BMI for women who have history of preeclampsia 25.0 ± 4.8 kg/m^2 [9]. Obesity, a risk factor for preeclampsia, was able to increase the risk for preeclampsia by 2.47 times, was associated with insulin resistance, and was also associated with cardiovascular disease [15]. This would have an impact on kidneys either damage to the kidney structure or a decrease in glomerular filtration rate (GFR).

As to the parity characteristics, primigravida was found in 11 subjects (35.5%), secundigravida (Nullipara) was found in 1 subject (3.1%), secundigravida was found in 4 subjects (12.9%), and multigravida was found in 15 subjects (48.42%). Ilhami et al., found that the mean of parity for pregnant women with preeclampsia was 0.61 ± 0.93 [11]. First pregnancy/ Nulipara was a significant risk factor for preeclampsia, which was almost 3 times higher risk [16].

The characteristics of the onset when diagnosis of preeclampsia was established, were being divided into early onset in 19 subjects (61.3%) and late onset in 12 subjects (38.7%). Based on the onset of preeclampsia, it was divided into early onset preeclampsia (<34 weeks) and late onset preeclampsia (≥ 34 weeks) [17]. Veronica et al. conducted a study on 775 patients with history of preeclampsia, and found that the mean of gestational age at delivery was $33^{+3} \pm 3^{+5}$ [9]. Anna et al. conducted a retrospective study on 214 pregnant women with preeclampsia, and found 113 women (52.8%) with early onset preeclampsia and 101 women (47.2%) with late onset preeclampsia [18]. Early onset preeclampsia was associated with placental abnormalities with failure of remodelling a. spiralis and decreased uteroplacental blood flow, whereas late onset preeclampsia was more associated with extrinsic and maternal factors such as diabetes, multiple pregnancies, maternal hypoxia, anemia, and obesity [17].

There were 6 subjects (19.35%) in prehypertension group, 19 subjects in stage I hypertension (61.29%), and 6 subjects in stage II hypertension (19.35%). This indicated that there was incidence of chronic postpartum hypertension in women who had history of preeclampsia with severe fetures. Cohort's study in Denmark on more than 500,000 deliveries showed that history of preeclampsia increased the risk of chronic hypertension 3.61-times higher (95% CI, 3.43-3.80) [19]. The guidelines of American College of Obstetricians and Gynecologist (ACOG) explained that the blood pressure in women with preeclampsia usually dropped within 48 hours after giving birth, but it increased again in 3-6 days postpartum. Meanwhile, regarding hypertension in women without a history of hypertension before pregnancy, NICE said that hypertension would resolve in 6 to 12 weeks postpartum [20].

This study found that there was persistent proteinuria both in the interval group of 4 - ≤13 months postpartum and the group of >13 - 24 months postpartum. The mean of proteinuria levels before delivery was +3 which lowest level was +1 and highest level was +3; while the mean of proteinuria levels after delivery was +1 which lowest levels was 0, highest levels was +3, and p value was 0,000. This suggested that women who had history of preeclampsia with severe features did not fully experience resolution, there was still persistent proteinuria that could affect their renal function. Proteinuria is a strong predictor of chronic kidney disease. Greater proteinuria indicates a higher risk for progression of chronic kidney disease.

The means of serum creatinine levels in the two groups at the postpartum interval were still within normal limits, but there was an increase in the mean of serum creatinine levels in interval group of >13 to 24 months postpartum i.e. 0.85 ± 0.23 mg/dl. The mean of serum creatinine levels before delivery was 0.69 ± 0.15 mg/dl and that of after delivery was 0.83 ± 0.22 mg/dl, with p value 0.009. A diagnosis of preeclampsia associated with kidney diseases is established when serum creatinine levels was found above 1.1 mg/dl or when there was an increase in serum creatinine levels before a condition where there were no other kidney disorders [21, 22]. Manjareeka et al., found that the mean of serum creatinine levels was 0.72 ± 0.39 mg/dl [23]. In this study, there was an increase in mean of serum creatinine levels before and after delivery, but the increase did not exceed normal reference value. This was related to the slow and chronic course of chronic kidney disease, so that an insignificant increase in serum creatinine occurred.

There was also a decrease in GFR in the interval group of >13 to 24 months postpartum compared to the group of 4 to ≤13 months postpartum. Veronica et al. obtained the mean of GFR on 775 women with history of preeclampsia, 105 ± 15 in mean of interval of 10 months (6-18) postpartum [9]. The findings in this study suggested that the damage that occurred was still in the early stages of chronic kidney disease, which occurred slowly but surely there would be a progressive decline in nephron function. This condition progressed slowly and

became chronic naturally, so it was necessary to periodically follow-up for these patients.

The classification of CKD according to KDIGO was divided into 5 stages based on GFR with the presence or absence of kidney damage. The most commonly used GFR estimation equation was the Cockcroft and Gault Formula by considering serum creatinine levels, age, body weight, sex, and race. At stage 1-3, there were usually no symptoms (asymptomatic). Clinical manifestations appeared in low renal function, which was seen at stage 4 and 5 [24]. In this study, stage I of chronic kidney disease was found in 23 subjects (74.2%) with the mean of GFR of 107.08 ± 22.86 ml/min/1.73 m^2. Stage II of chronic kidney disease was found in 8 subjects (25.8%) with the mean of GFR 78.30 ± 9.2 ml/min/1.73 m^2. In fact, this study also found stage II of chronic kidney disease (CKD) was found at the interval group of 4 to ≤13 months postpartum in 4 subjects. This suggested that longer occurrence of persistent postpartum renal impairment will decrease renal function. Most of the causes of CKD were irreversible with the course of life, and treatment was aimed at slowing the progression to kidney failure [24, 25].

The mean of glomerular filtration rate which was not significant between group of history of early onset preeclampsia was 103.07 ± 25.23 ml/min/1.73 m^2 and group of history of late onset preeclampsia was 113.40 ± 28.24 ml/min/1.73 m^2. Early onset preeclampsia more often causes severe clinical cases than the late onset. Anna et al. studied 231 preeclampsia patients comprehensively regarding the changes that occurred in early onset and late onset preeclampsia. There were significant different neurological complications, hemolysis events, and FGR in the early onset group compared to the late onset group. Meanwhile, in the condition of proteinuria, renal insufficiency, changes in hepatic function, hematological complications (thromboc ytopenia and DIC), there were no significant differences in both groups [18]. Due to the absence of significant differences in kidney damage in the two groups, the early onset and late onset groups were equally at risk for postpartum chronic kidney disease. This was in line with the results of this study which showed that there was no significant difference in the glomerular filtration rate after delivery in both groups.

CONCLUSIONS

There was a tendency of decreased renal function in women with a history of preeclampsia with severe features with the findings of persistent proteinuria from more than 3 months to 2 years postpartum, and an increase in mean of serum creatinine levels before and after delivery, and a decrease in GFR, but it was not significant. This was related to the slow course of chronic kidney disease so that a periodical follow-up had to be carried out to prevent further kidney disorders.

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