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RESEARCH

Comparison on the Incidence of Blood Pressure Increase in the Second Trimester Based On Glomerular Filtration Rate (GFR)

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Abstract

During normal pregnancy, glomerulus filtration rate (GFR) is increased so that the concentration of urea and creatinine decreased. With the onset of hypertension in pregnancy, renal perfusion and glomerular filtration decreases, the greater of decline showed more severe illness. This was an observational analytic study with Cohort design and performed in Obgyn Department of M. Djamil Hospital Padang, general district hospital in Batusangkar and Achmad Mukhtar, Private Practice Midwife in Batusangkar from June-December 2014. 100 samples of first trimester of pregnancy, each subject were examined ureum, creatinine, cystatin-c and glomerular filtration rate (GFR) based on CKD-EPI Cystatin and Creatinine 2012 Equation formula. Then divided into two groups, high glomerular filtration rate (GFR) high and low glomerular filtration rate (GFR) group. Each subject was evaluated blood pressure every 3 weeks and statistical analysis was done using the Independent samples test and chi square. There was significant association difference in the levels of urea, creatinine and cystatin-c between high GFR group and low GFR group ($p < 0.05$). There was a statistically significant relationship between low GFR group of pregnant women with changes in systolic and diastolic blood pressure that persists or increases of 5-10 mmHg ($p < 0.05$).

Keywords: Preeclampsia, glomerular filtration rate (GFR), ureum, creatinine, cystatin-c, blood pressure

INTRODUCTION

Preeclampsia is defined as a condition of hypertension and proteinuria after 20 weeks' gestation. Preeclampsia is a major pregnancy complication where its incidence is increasing worldwide and is associated with maternal morbidity and mortality. Preeclampsia affects 3%-5% of all pregnancies and have caused an estimated 60,000 maternal deaths worldwide each year. At RSUP Dr. M. Djamil Padang in the period of 1998-2003, the incidence of preeclampsia was 5.5% (663 cases) and eclampsia was 0.88% (106 cases) of 12,034 deliveries. Data from medical records of patients treated in the Obstetrics and Gynecology Section of RSUP Dr. M. Djamil Padang from January 1 to December 31, 2010 found 176 cases of preeclampsia and eclampsia, 140 cases were severe preeclampsia, 36 cases were eclampsia, and 3 cases of death due to eclampsia.^{1,2,3,4}



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In normal pregnancy significant changes occur, both in the structure and function of the urinary tract. Urinary tract dilation is one of the most frequent anatomic changes caused by pregnancy. These changes cause dilation of the ureter and calyx and renal pelvis.⁵

Glomerular filtration rate and renal blood flow increase by approximately 35-50% during normal pregnancy. Creatinine clearance on average increases immediately after the first day of the last menstrual period, significantly increasing in the 4th week of pregnancy. Starting in about 4 weeks, renal hyperemia decreases. Glomerular filtration rate increases during pregnancy, serum creatinine and blood urea decrease. Uric clearance increases and serum uric acid decreases. Urinary protein excretion increases, also there may occur mild microalbuminuria. Women with inactive chronic glomerulonephritis, before pregnancy protein excretion <1 g/ day, 2-6 grams of protein excretion in urine during normal pregnancy due to glomerular hyperemia without other signs of exacerbation nephritis.⁶

Recently a new marker has been developed in evaluating glomerular filtration rate by measuring cystatin-c levels in serum. Cystatin-c is a nonglycosylate-based protein that is constantly produced by all nucleated cells. Cystatin-c is free of filtration in the glomerulus and catabolized in the renal tubules thus it is not secreted or reabsorbed as an intact molecule. Because serum cystatin-c levels are independent of age, sex and muscle mass, cystatin-c can be used as a better marker than serum creatinine levels in measuring glomerular filtration rate. Serum cystatin-c can be used as a function test in the kidney because it is simpler, sensitive and good screening for detecting renal insufficiency.^{7,8}

Two meta-analyses have concluded that serum cystatin-c is superior to serum creatinine as a marker of kidney function. However, recent findings have indicated an equation that uses serum creatinine and serum cystatin-c with age, sex, and race will be better than an equation that only uses one of these serum markers.⁹

Coll in his research found that serum cystatin-c began to rise above the normal value of GFR 88 ml/ min, whereas serum creatinine only began to increase when GFR dropped to 75 ml/ min. On mild decline in kidney function (GFR 50-83 ml/ min), cystatin-c was increased in 100% of patients, whereas serum creatinine only increased in 75% of patients. Newman et al. in its study of 469 patients concluded that besides being a better marker of GFR than serum creatinine, cystatin-c was also a marker that was more sensitive to small changes in GFR. On mild kidney function decline, cystatin-c increased in 71.4% of patients, whereas serum creatinine only increased in 52.45 patients.¹⁰

Cystatin-c equation for measuring the estimated GFR ¹¹ :

- CKD which is not affected by age, sex and race
- eGFR: $76.7 \times \text{Cystatin-c}^{-1.19}$
- CKD which is affected by age, sex and race
- eGFR: $127.7 \times \text{cystatin-c}^{-1.17} \times \text{age}^{-0.13} \times 0.91$ (if female) $\times 1.06$ (if African American)
- CKD influenced by serum creatinine, cystatin-c, age and race



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- $eGFR: 177.6x Cr^{-0.65} \times cystatin-c^{-0.57} \times age^{-0.20} \times 0.80$ (if female) $\times 1.11$ (if African American)

Bailey and Rollensto, found that kidneys grew a little 1.5 cm longer during the early puerperium than 6 months later. During normal pregnancy, renal blood flow and glomerular filtration speed increase. With the onset of preeclampsia, renal blood perfusion and glomerular filtration rate decrease. This is caused by changes in the kidneys, which are most likely to occur due to severe vasospasm. Most women with mild to moderate preeclampsia, a decrease in plasma volume will cause a decrease in glomerular filtration and cause plasma creatinine values to increase two times greater than normal pregnancies around 2-3 mg/ dl (normal: 0.5 mg/ dl).¹²

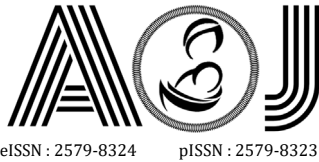
Taufield et al reported that preeclampsia, which occurs together with decreased urinary potassium excretion, occurs due to increased reabsorption in the tubules. This explains the decrease in calcium excretion in hypertensive pregnant women. After delivery if there is no chronic renovascular disease as the underlying disease, improvement in kidney function can usually occur immediately.¹²

Impaired renal function is an important component of the pathophysiology of preeclampsia in addition to endothelial dysfunction and placental hypoperfusion. Close monitoring of kidney function is very important to ensure optimal delivery time to prevent kidney damage.^{13,14} The main place of kidney injury in preeclampsia is endothelial glomerular cells. Glomerular endothelial dysfunction is characterized by disorders of GFR, hypertension and proteinuria. Glomerular dysfunction is characterized by decreased GFR, proteinuria and hypertension.¹⁵

Other biochemical markers that have been used in the diagnosis and monitoring of preeclampsia are serum creatinine and gout. However, the use of serum creatinine as a marker of GFR is limited by the influence of each individual's muscle mass. In addition, renal vasodilation in pregnancy causes a 50-80% increase in plasma flow and changes in GFR, which further complicates the use of serum creatinine as a marker of GFR in pregnancy.¹⁴ During pregnancy an increase in renal plasma GFR flow $\geq 40\%$ of non pregnant women.¹³

Healthy pregnant women show glomerular hyperfiltration. During the second half of pregnancy there is an increase in GFR above the normal value.¹⁶ Hyperfiltration is caused by a disruption in plasma oncotic pressure that flows along the glomerular capillaries. Oncotic pressure is the force that opposes the formation of glomerular filtration. Reduction of oncotic pressure in pregnancy is caused by 2 phenomena, the first is hypervolemic hemodilution which decreases protein concentration and plasma oncotic pressure that enters glomerular circulation, the second is high flow of renal perfusion.¹⁵

Glomerular filtration rate usually increases during pregnancy, in preeclampsia it is characterized by a decrease in glomerular filtration rate. This decrease in kidney function



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needs to be monitored to determine the time of delivery before serious kidney damage occurs. Glomerular filtration rate reflects the level of glomerular endotheliosis due to a reduction in the number and size of endothelial fenestrae that will damage the glomerular permeability pressure.¹¹

In women with preeclampsia, glomerular endotheliosis is higher in patients with gestational hypertension or in normal pregnancies. The rate of glomerular endotheliosis represents the severity of preeclampsia.¹¹

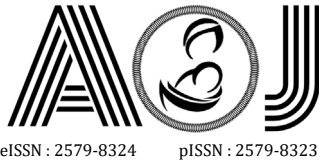
METHOD

This research was conducted with an observational analytic method with a prospective cohort design at the Obgyn Polyclinic of RSUP Dr. M. Djamil Padang, Batusangkar Regional General Hospital, Achmad Mukhtar Regional General Hospital, and Private Practice Midwives in Batusangkar from June 2014 to December 2014. From 100 research samples of first trimester pregnancy, each subject was examined for ureum, creatinine, cystatin-c and glomerulus filtration rate (GFR) based on CKD-EPI Cystatin and Creatinine 2012 Equation. Then divided into 2 groups, namely high glomerular filtration rate (LFG) ($\geq 150 \text{ ml/min/1.73m}^2$) and low ($< 150 \text{ ml/min/1.73m}^2$). Blood pressure evaluation is done every 3 weeks, if hypertension is obtained then followed by urine protein examination. Follow up to the patient was stopped if the pregnancy was complete 22 weeks or a diagnosis of preeclampsia and gestational hypertension was established. Statistical analysis to assess significance using the Independent samples test and chi square on SPSS 22.0 for windows.

RESULTS**Basic Characteristics of Research Subjects**

The study was conducted from June 2014 to December 2014 in Batusangkar Regional Hospital (27), Achmad Mukhtar Regional Hospital (5), Dr. M. Djamil General Hospital (10), and private practice midwives (67) with a total of 109 research subjects included in the study inclusion criteria, divided into 56 people high GFR group and 53 people of low group. 9 of these samples were declared to be dropped out (DO) where during the trip 3 people from the low GFR group experienced abortion and 6 people from the high GFR group experienced abortion (2 people), move out (2 people) and cannot be contacted, never came again for antenatal visits (2 people). The research subjects sampled in the study were 100 people and were divided into 2 groups, groups with low glomerular filtration rate (GFR) by 50 patients and high glomerular filtration rate by 50 patients. The basic characteristics of the research subjects are shown in table 1.

There were no statistically significant differences in baseline characteristics in the two groups of pregnant women with low GFR and high GFR except for differences in age and



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parity. In the group of pregnant women with low glomerular filtration rates, the mean age was 29.36 ± 5.232 and parity 2.54 ± 1.581 .

The mean trimester I systolic blood pressure (antenatal care) in the group of pregnant women with low glomerular filtration rate and groups with high glomerular filtration rates were $112.60 \pm 5,997$ and $109.80 \pm 8,449$. The mean trimester I ANC (antenatal care) diastolic blood pressure in the group with low glomerular filtration rate and the group with high glomerular filtration rate were 72.60 ± 5.272 and 71.60 ± 5.481 .

Table 1. Basic Characteristics of Research Subjects

Demography	GFR (Low) n = 50	GFR (High) n = 50	p
Age (yrs \pm SD)	29.36 ± 5.232	25.68 ± 4.470	0.000
Parity (times \pm SD)	2.54 ± 1.581	1.86 ± 0.756	0.007
Systolic Blood Pressure ANC (mmHg \pm SD)	112.60 ± 5.997	109.80 ± 8.449	0.059
Diastolic Blood Pressure ANC (mmHg \pm SD)	72.60 ± 5.272	71.60 ± 5.481	0.355

Characteristics of Laboratory Research Subjects**Table 2.** Metabolic Characteristics of Research Subjects

Laboratory	GFR (Low) n = 50	GFR (High) n = 50	p
Ureum (mg/dl \pm SD)	27.23 ± 14.237	15.87 ± 6.936	0.000
Creatinine (mg/dl \pm SD)	0.70 ± 0.204	0.47 ± 0.071	0.000
Cystatin-C (mg/dl \pm SD)	0.68 ± 0.123	0.44 ± 0.068	0.000

Table 2 shows the average value of each laboratory examination on the research subjects. There was a statistically significant difference in the levels of ureum, creatinine and cystatin-c of trimester I pregnant women in the group of pregnant women with low glomerular filtration rate (GFR) and high glomerular filtration rate (GFR). Average urea level, creatinine and cystatin-c trimester I pregnant women were higher in the group of pregnant women with low glomerular filtration rate (GFR) compared to the levels of ureum, creatinine and cystatin-c in the group of pregnant women with high glomerular filtration rate (GFR) (p 0.00).

A description of the urea level of trimester I pregnant women in the group of pregnant women with low glomerular filtration rate (GFR) and high GFR can be seen in Figure 1.

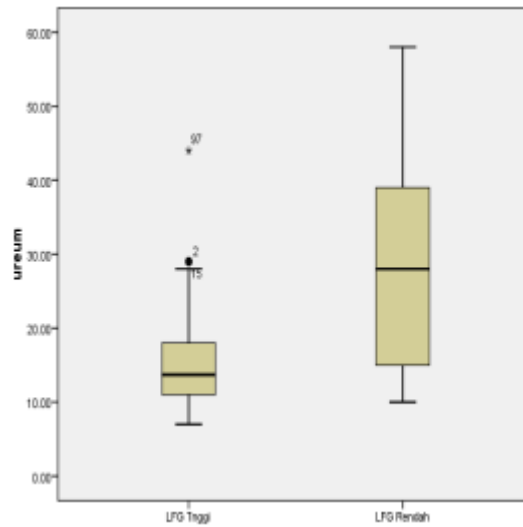


Figure 1. Uremia Trimester I levels in the GFR low group and high GFR

From Figure 1, it can be seen that in this study the occurrence of low glomerular filtration rate (GFR) was more common in trimester I pregnant women with ureum levels > 27 mg/ dL (27.23 ± 14.237), this result was statistically significant ($P < 0.05$). There were three (*) first trimester pregnant women in the high glomerular filtration rate (GFR) group having ureum levels of more than 27 mg/ dL i.e. samples number 2, 15 and 103 with blood ureum levels of more than 27 mg/dL i.e. samples number 2 and 15, while sample number 103 obtained ureum levels of 44 mg/ dL.

An overview of creatinine levels in first trimester pregnant women in the group of pregnant women with low glomerular filtration rate (GFR) and high GFR can be seen in Figure 2.

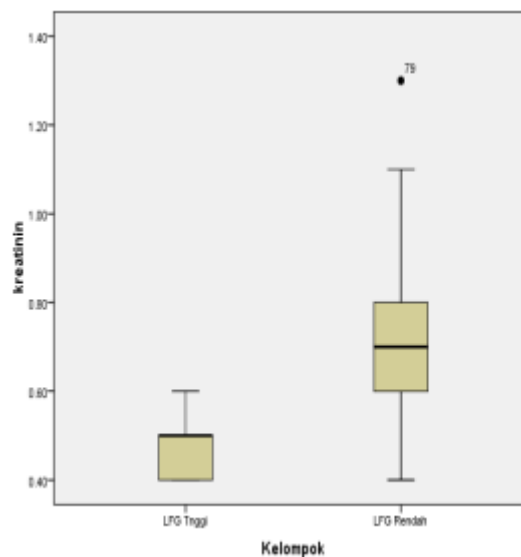
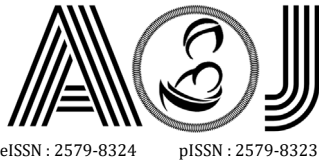


Figure 2. Trimester I Creatinine levels in low GFR group and high GFR



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From Figure 2, it can be seen that in this study the occurrence of low glomerular filtration rate (GFR) is more common in trimester I pregnant women with creatinine levels > 0.7 mg/ dL (0.70 ± 0.204), this result was statistically significant ($P < 0,05$). There was one (*) trimester I pregnant woman in the glomerular filtration rate (GFR) group having a creatinine level of more than 0.7 mg/ dL, i.e. sample number 84 (appendix 8) with blood creatinine levels of 1.3 mg/ dL.

Relationship between Glomerular Filtration Rate and Change in Blood Pressure in Trimester II

The relationship of glomerular filtration rate in a group of patients with low glomerular filtration rate in trimester I to changes in blood pressure in trimester II is shown in table 3.

Table 3. Clinical Characteristics of Research Subjects

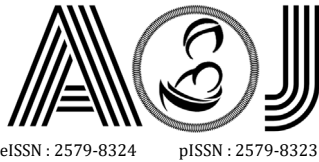
		GFR		Total
		High n(%)	Low n(%)	
TD	decrease	41(82%)	15 (30%)	56 (56%)
	increase	9 (18%)	35 (70%)	44 (44%)
	Total	50 (100%)	50 (100%)	100 (100%)

Statistical analysis with the chi-square test found a significant relationship between pregnant women with low glomerular filtration rate (GFR) with changes in systolic and diastolic blood pressure that persisted or increased by 5-10 mmHg with a p value ($0.00 < 0.05$). Table 3 shows the relative risk (RR) for the cohort of 3.89.

DISCUSSION

Analysis of the basic characteristics of the sample data in this study showed the results of the occurrence of low glomerular filtration rate (GFR) was more common in trimester I pregnant women aged 29-30 years (29.36 ± 5.232) and parity of more than 3 (2.54 ± 1.581), this result was significant statistically ($P < 0.05$). According to Pusparini, 2005 in a Cross Sectional study on GFR explained the examination of blood creatinine and creatinine clearance was influenced by gender, age, and body mass index (BMI). While cystatin-c examination is not influenced by gender, age, inflammatory processes, heat and body mass index (BMI).¹⁷ The sample in this study assessed GFR in the first trimester using a combination of serum creatinine and cystatin-c, because serum cystatin-c levels do not depend on age, sex and muscle mass so they can be used as better markers in measuring glomerular filtration rate.⁷

A study published in 2008 on the function of GFR at the beginning of 4 weeks postpartum in 57 women with preeclampsia compared with healthy postpartum controls, found GFR decreased by 40% on the first day of postpartum and only decreased by 19% and 8% in the second and fourth week of postpartum.¹⁸ According to the literature, kidney



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changes during pregnancy are also influenced by the hormone progesterone, resulting in an increase in renal plasma flow, hydroureter and physiological hydronephrosis in pregnancy. All changes that occur will return to normal after 8-12 weeks after giving birth.¹⁹ After delivery if there is no chronic renovascular disease as the underlying disease, improvement in kidney function can usually occur immediately.¹²

In this study, the existence of significant differences in the characteristics of age and parity did not significantly affect the group of pregnant women whose glomerular filtration rate will be examined in the first trimester (initial visit), so it can be concluded that this study can be continued.

The results of data analysis of the basic characteristics of the samples in this study showed that the results of the glomerular filtration rate (GFR) low were more common in trimester I pregnant women who had systolic blood pressure ANC trimester I > 110 mmHg ($112.60 \pm 5,997$) and diastolic blood pressure ANC trimester I > 70 mmHg ($72.60 \pm 5,272$), these results were not statistically significant ($P > 0.05$). Mauntquin JM, et al (1985) conducted a study on pregnant women with a gestational age of 9-12 weeks. From the results of blood pressure measurements, which increased between 130/80 mmHg to 135/85 mmHg, the sensitivity was 26% -57%, and specificity by 75% -98%. They concluded that early vasospasm that occurs in women with 9-12 weeks' gestation, tends to be preeclampsia.²⁰

Another study conducted by Broughton P, et al (1998) conducted research on 212 nulliparous women, under 20 weeks' gestation, and approaching 28 weeks' gestation. They concluded that a single examination of systolic blood pressure of 140 mmHg or more before 20 weeks' gestation increases the risk of hypertension caused by pregnancy and preeclampsia. Michelle Berlin, Eugene Washington (1996) recommended that blood pressure measurements be taken for all pregnant women at the time of the first antenatal visit as a screening for possible preeclampsia.^{21,22}

The results of data analysis of the characteristics of the urea level of trimester I pregnant women showed that there were differences in the levels of urea level of trimester I pregnant women in the group of pregnant women with low glomerular filtration rate (GFR) and high glomerular filtration rate (GFR). From these results the incidence of low glomerular filtration rate (GFR) was more common in trimester I pregnant women with ureum levels > 27 mg/ dL (27.23 ± 14.237), these results were statistically significant ($P < 0.05$). There were three trimester I pregnant women in the high glomerular filtration rate (GFR) group having ureum levels of more than 27 mg/ dL, namely sample numbers 2, 15 and 97 with blood urea levels of 29 mg/ dL in sample numbers 2 and 15, while sample numbers 97 obtained ureum levels of 44 mg/ dL.

Analysis of the characteristics of creatinine levels in trimester I pregnant women showed that there were differences in creatinine levels in trimester I pregnant women in the group of pregnant women with low glomerular filtration rate (GFR) and high glomerular



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filtration rate (GFR). From these results it was found that the low glomerular filtration rate (GFR) was more common in trimester I pregnant women with creatinine levels > 0.7 mg/ dL (0.70 ± 0.204), this result was statistically significant ($P < 0.05$). There was one trimester I pregnant woman in the glomerular filtration rate (GFR) group having a creatinine level of more than 0.7 mg/ dL, sample number 79 with blood creatinine level of 1.3 mg/ dL.

According to the literature, an increase in plasma creatinine levels as high as 0.5 mg/ dl means a 40% change in glomerular velocity. Normal creatinine levels in plasma vary with the laboratory and the method used, but never higher than 1.5 mg/ dl. If kidney damage is advanced, small changes in the value of creatinine clearance cause noticeable changes in plasma creatinine levels.²³

Creatinine is the final product of creatine metabolism. Creatine is mainly synthesized by the liver and almost all of it is present in skeletal muscle which is reversibly bound to phosphate in the form of phosphocreatin, which is an energy storage compound. The keratin + phosphate reaction produces phosphocreatin. However, a small portion of this keratin is irreversibly turned into creatinine that has no function. The amount of creatinine that is formed is proportional to the mass of skeletal muscle. Skeletal muscle activity does not have much effect. Male reference values are 0.6-1.3 mg/ dl, and for women 0.5-1 mg/ dl serum. The amount of creatinine that is formed in a day does not change much, unless a lot of muscle tissue is damaged at once by trauma or by disease. The kidneys can secrete creatinine without difficulty. Unlike the ureum, reduced blood and urine flow does not greatly change creatinine excretion, because brief changes in blood and glomerular function can be offset by increased creatinine secretion by the tubules. Ureum in the blood rises faster than creatinine when kidney function decreases.²³

Healthy pregnant women show glomerular hyperfiltration. Hyperfiltration is caused by a disruption in plasma oncotic pressure that flows along the glomerular capillaries. Oncotic pressure is the force that opposes the formation of glomerular filtration. Reduction of oncotic pressure in pregnancy is caused by 1 phenomenon, the first is hypervolemic hemodilution which decreases protein concentration and plasma oncotic pressure that enters glomerular circulation, the second is high flow of renal.¹⁵

In women with glomerular endotheliosis preeclampsia is higher in patients with gestational hypertension or in normal pregnancies. The rate of glomerular endotheliosis represents the severity of preeclampsia. Taufield et al (1987) reported that preeclampsia, which occurs together with a decrease in urinary potassium excretion, occurs due to increased reabsorption in the tubules. This explains the decrease in calcium excretion in hypertensive pregnant women. With the onset of preeclampsia renal blood perfusion and glomerular filtration rate decreases. This is caused by changes in the kidneys, which are most likely to occur due to severe vasospasm. Most women with mild to moderate preeclampsia, a decrease in plasma volume that will cause a decrease in glomerular filtration and cause



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plasma creatinine values to increase two times greater than normal pregnancies around 2-3 mg/ dl (normal: 0.5 mg/ dl).^{11,12}

The results of this study indicated that there was a significant relationship between groups of pregnant women with low glomerular filtration rate (GFR) with changes in systolic and diastolic blood pressure that persist or increase by 5-10 mmHg. Cohort research by Ferry Sabarudin done previously in RSUP. DR. M. Djamil Padang July 2005-March 2006 regarding the relationship of systolic blood pressure and urine creatinine calcium ratio of 16-20 weeks pregnant women with the incidence of preeclampsia, obtained the probability of the occurrence of preeclampsia/ eclampsia based on systolic blood pressure group 120-139 mmHg, 6.19 times greater than the systolic blood pressure group <120 mmHg.

According to the literature, the glomerular filtration rate usually increases during pregnancy, by 40% to 65%, as a result of an increase of up to 80% of renal blood flow in the early second trimester and subsequently maintained until the middle of the third trimester. Glomerular filtration rate reflects the level of glomerular endotheliosis due to a reduction in the number and size of endothelial fenestrae that will damage the glomerular permeability pressure.¹¹

Statistical analysis with the chi-square test found a significant relationship between pregnant women with low glomerular filtration rate (GFR) with changes in systolic and diastolic blood pressure that persisted or increased by 5-10 mmHg with a p value (0.00) <0.05. From this study it is known that the relative risk (RR) for the cohort is 3.89. This shows that the group of pregnant women with low glomerular filtration rate had a relative risk of 3.89 times experiencing an increase in systolic and diastolic blood pressure of 5-10 mmHg than in the group of pregnant women with high glomerular filtration rate.

CONCLUSION

There are differences in levels of urea, creatinine and cystatin-c of trimester I pregnant women in the group of pregnant women with low GFR and high GFR. First trimester pregnant women with low glomerular filtration rate (GFR) are more common in trimester I pregnant women with ureum levels > 27 mg/ dL, creatinine > 0.7 mg/ dL and cystatin-c > 0.68 mg/ L. There is a significant relationship between the group of pregnant women with low glomerular filtration rate (GFR) with changes in systolic and diastolic blood pressure that persist or increase by 5-10 mmHg with a p value (0.00) <0.05 and a known relative risk (RR) for a cohort of 3.89.



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