

Research Article

Long-term Outcomes of Severe Preeclampsia Cases: Cross – Sectional Study

Keluaran Jangka Panjang Kasus Preeklamsia Berat: Studi Potong Lintang

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Abstract

Objective: to know the long term outcomes on severe preeclampsia mother by clinically and laboratory, and the long term outcome of the baby that she delivered.

Methods: This is a cross sectional study was conducted at Obstetrics Outpatient Clinic Dr. Cipto Mangunkusumo General Hospital (Cipto Mangunkusumo NCGH) on January–June 2017, of patients with previous severe preeclampsia that gave birth in Cipto Mangunkusumo NCGH on January 2014 – December 2016, and was descriptively analyze using SPSS Statistics 24.

Results: One hundred and twenty seven patients were studied, divided into 3 groups of post – delivery time which were 6 months, 12 months, and 24 months. The 6 months' group, mean of blood pressure were 147/92 mmHg (SD 38/SD 39), BMI 29 kg/m² (SD 6), CRP level 16.6 mg/l (0.3–42.60) and urine protein dipstick 1 (0 – 3). The 12 months' group, mean of blood pressure were 112/88 mmHg (SD 12/SD 24), BMI 21 kg/m² (SD 7), CRP level 12.7 mg/l (3.4 – 15.2) and urine protein dipstick 0 (0 – 3). The 24 months' group, mean blood pressure 154/95 mmHg (SD 45/SD 62), BMI 28.83 kg/m², CRP level 14,2 mg/l (SD 8.54) and urine protein dipstick 0 (0 – 3). Meanwhile, the long – term outcome of babies that 68% baby were born with preterm condition and mean birth weight were 1943 grams (SD 1245), the 5th minute Apgar score >7 were 63.78%, and only 44.88% baby had normal growth development.

Conclusion: It The long – term outcome patients with previous severe preeclampsia are blood pressure, BMI, and CRP level still high, and negative urine protein level until 2 years of post – delivery. The long – term outcome of the babies that delivered were on preterm condition and low birth weight, with less than 50% had normal growth and development.

Keywords: c–reactive protein, growth and development, proteinuria, post–delivery, severe preeclampsia.

Abstrak

Tujuan: Untuk mengetahui keluaran jangka panjang pada pasien ibu PEB dari sudut klinis dan laboratoris, serta keluaran jangka panjang bayi yang dilahirkan.

Metode: Penelitian ini menggunakan desain potong lintang terhadap pasien riwayat PEB yang pernah melahirkan di RSUPN Dr. Cipto Mangunkusumo pada bulan Januari 2014–Desember 2016. Subjek diminta datang ke Poli Obstetri RSUPN Dr. Cipto Mangunkusumo pada Januari–Juni 2017 untuk dilakukan pemeriksaan klinis dan laboratoris (CRP dan protein urin), serta dilakukan analisa deskriptif menggunakan SPSS Statistik 24.

Hasil: Sebanyak 127 pasien yang diteliti terbagi dalam 3 kelompok yaitu pasien riwayat PEB setelah persalinan 6 bulan (kelompok I), 12 bulan (kelompok II), dan 24 bulan (kelompok III). Kelompok I didapatkan rerata tekanan darah (TD) 147/92 mmHg (SD 38/SD 39), IMT 29 kg/m² (SD 6), kadar CRP 16,6 mg/l (0,3 – 42,60) dan protein urin 1 (0 – 3). Kelompok II didapatkan rerata tekanan darah (TD) 112/88 mmHg (SD 12/SD 24), IMT 21 kg/m² (SD 7), kadar CRP 12,7 mg/l (3,4 – 15,2) dan protein urin 0 (0 – 3). Kelompok III rerata TD 154/95 mmHg (SD 45/SD 62), IMT 28,83 kg/m², dengan rerata kadar CRP 14,2 mg/l (SD 8,54) dan protein urin 0 (0 – 3). Sedangkan keluaran jangka panjang bayi yang dilahirkan bahwa 68% lahir dengan kondisi preterm dengan rerata berat lahir 1.943 gram (SD 1.245), nilai Apgar menit ke-5 >7 63,78%, dan hanya 44,88% tumbuh – kembang bayi normal.

Kesimpulan: Gambaran keluaran jangka panjang pasien riwayat PEB didapatkan tekanan darah, IMT dan kadar CRP masih tinggi, serta protein urin urin negatif setelah 2 tahun setelah persalinan. Keluaran jangka panjang bayi yang dilahirkan mayoritas kondisi preterm dan berat lahir rendah, dengan kurang dari 50% bayi tumbuh – kembang normal.

Kata kunci: c–reactive protein, preeklamsia berat, proteinuria, setelah persalinan, tumbuh kembang bayi.

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INTRODUCTION

Preeclampsia has been one of the leading causes of maternal and perinatal morbidity and mortality and complicates 2-8% pregnancies worldwide.^{1,2} Since 2013, the definition and diagnostic criteria for preeclampsia is upgraded and modernized by ACOG Task Force and removing proteinuria as an absolute criteria for diagnosing a preeclampsia. The latest guidelines from ACOG, preeclampsia is divided into 2 criteria with and without severe feature.¹

Among several risk factors of preeclampsia, age > 35 years old and Body Mass Index > 30, are prone to have preeclampsia and preterm labor, also increasing cardiovascular disease and diabetes mellitus incidents in later days.¹⁻³ Short-term and long-term complication can also happen to preeclampsia patients and the baby delivered, that caused by endothelial dysfunction that led to blood flow uteroplacental insufficiency.¹⁻³ Maternal complications are metabolic syndrome (obesity, chronic hypertension, cardiovascular disease, cerebrovascular disease, renal dysfunction) and risk of preeclampsia in the next pregnancy.^{2,4-11} Meanwhile neonatal complications are metabolic syndrome and growth – development impairment (eg. cognitive function).^{2,12,13}

CRP is one of systemic biomarker and acute phase protein that respond to inflammation, have been studied as predictive factor of complication of severe preeclampsia in pregnancy and outcome for maternal and neonatal in later days.¹⁴⁻¹⁷ Many studies of CRP levels found increasing during pregnancy with preeclampsia.¹⁷⁻¹⁹ One of the studies found that there is persistent increasing of high sensitivity – CRP (hsCRP) of 5 – 8 years after delivery in preeclampsia group than control group.¹⁸ Others showed that meanwhile from 255 patients, 50 patients are having recurrence; with baseline CRP concentration between patients with preeclampsia recurrence and not having recurrence are almost the same, and not correlated with preeclampsia recurrence.²⁰

Until today Indonesia do not have many studies about long term outcomes of severe preeclampsia cases, by clinical and laboratories. Due to this encourage us to study about long – term outcomes maternal and neonatal of severe preeclampsia from 6 months, 1 year, and 2 years after delivery.

The purpose of our study was to describe the long term outcomes on patients with history of severe preeclampsia by clinically and

laboratories, and the long term outcomes of the baby she delivered.

METHODS

This was a cross – sectional study of patients with previous severe preeclampsia (using former diagnostic criteria for preeclampsia) that gave birth in Dr. Cipto Mangunkusumo NCGH in January 2014 – December 2016. Subjects were called to come to our Obstetrics Outpatient Clinic on January– June 2017 and get examined (physical and laboratories exams of CRP and urine dipstick). Subjects were consecutively – collected until all the samples needed were fulfilled, were grouped into 3 group time of delivery (6 months, 1 year, and 2 year). Inclusion criteria were patients post-delivery with history of preeclampsia, willing to join the study, reachable by phone and willing to come as scheduled, and live in Jakarta, Bogor, Depok, Tangerang, and Bekasi (Jabodetabek) area. Exclusion criteria were symptomatic infection disease (upper respiratory tract infection, reproduction tract infection, urinary tract infection), subjects were pregnant during contacted by phone, subjects refused to join the study, subjects were moved out of town, subjects were deceased, and subjects were unreachable by phone number in medical records. Drop out criteria were if during study subjects were symptomatic infected, known or diagnosed pregnant during visit, and not able to finish the study.

From medical records we found subjects' location and phone number, were contacted to visit our Obstetric Out clinic, given informed consent and early screening (exclusion criteria) verbally. During visit to out clinic, subjects will be asked for sign up the informed consent, done the physical exam and protein urine dipstick examination by nurse and doctors on duty, continued with CRP examination at Out clinic Laboratory. Data of subjects and her baby (before delivery) were collected from medical records. Patients then interviewed about latest condition of the baby in time of study (age, latest condition, and growth development). This study has passed the Ethical Approval Faculty of Medicine University of Indonesia. All data were descriptively analyzed with SPSS Statistics 24. Data with normal distribution, reported in means and standard deviation. Data with abnormal distribution, reported in median, minimum value, and maximum value.

RESULTS

We managed to get 765 subjects from medical records to be contacted. From those subjects, 184 subjects were able to be contacted, fulfilling the inclusion criteria, and willing to come to our hospital. As scheduled, only 130 subjects that able to come and following the study. During study, 3 subjects got into drop out criteria due to 2 subjects known to be pregnant by physical examination and 1 subject did not able to finish the study (not done the CRP examination).

Based on 127 datas of subjects collected, the mean age of patients when diagnosed with severe preeclampsia were 29 years old (SD 8.7), mean of BMI were 32.8 kg/m² (SD 9.7) with 70% subjects were overweight – obesity, more than 50% gestational age were less than <37 weeks (61.42%), and almost all subjects were done the cesarean section (90.55%). Their blood pressure at first visit at that time were high (median 182/100 mmHg (abnormal distribution)), and urine protein were positive (median 1.5) (Table 1).

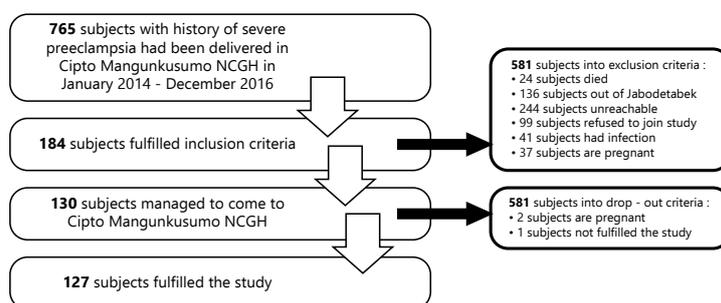


Figure1. Recruitment of subjects

Table1. Patients Characteristics

Variable	Mean (Standard Deviation)*	Median (Min – Max)**	n (%)
Age	29.3 (8.7)		
Parity		2 (1 – 5)	
Gestational age (weeks)	34.2 (6.3)		
< 37			78 (61.42)
37			49 (38.58)
Number of gestation (singleton/multiple)		1 (1 – 2)	
Mode of delivery			
Vaginal Delivery			10 (7.87)
Vacuum/Forceps Extraction			2 (1.57)
Cesarean section			115 (90.55)
Complication			
Yes			35 (27.56)
No			92 (72.44)
BMI first visit			
Underweight			2 (1.57)
Normoweight			36 (28.35)
Overweight – Obesity	32.8 (9.7)		89(70.08)
Systolic blood pressure first visit (diagnosed with severe preeclampsia)		182 (138 – 220)	
Diastolic blood pressure first visit (diagnosed with severe preeclampsia)		100 (80 – 145)	
Urine protein at first visit		1.50 (0 – 3)	

* Mean and standard deviation were used in normal distribution; ** Median and minimum/maximum value were used in abnormal distribution;*** n(%) was used in categoric value.

From 127 subjects collected, the mean of baby birth weight was 1943 grams (SD 1245), with 77.17% live at birth and 63.78% babies born with the fifth Apgar score were >7 (Table 2). The results from interviewing patients that 44.88%

babies delivered were in normal growth and development, 32.28% their weights were under the normal curve, and 22.84% babies were died (including intrauterine fetal death, still birth, and perinatal mortality before 24 months of age).

Table 2. Children's Subjects Characteristics

Variable	Mean (Standard Deviation)*	Median (Min – Max)**	n (%)
Birth weight (grams)			
< 2500	1943 (1245)		96 (75.59)
2500 – 4000			29 (22.83)
> 4000			2 (1.57)
The fifth Apgar Score			
0 – 7		9 (0 – 10)	46 (36.22)
8 – 10			81 (63.78)
At birth condition			
Live			98 (77.17)
Died			29 (22.83)
Children growth – development			
Normal			57 (44.88)
Weight under curve			41 (32.28)
Died before age 24 months			29 (22.84)

* Mean and standard deviation were used in normal distribution; ** Median and minimum/maximum value were used in abnormal distribution; *** N(%) was used in categoric value.

From physical examination, we found that patients with history of severe preeclampsia their blood pressure and BMI are still high. Meanwhile, from laboratories examinations, that until 2 years after delivery the CRP level were also high (> 5 mg/l) and the urine protein were back to normal level (Table 3).

Table 3. Physical Examination Results

Physical Examination	Time of Study		
	6 months (n = 54)	12 months (n = 38)	24 months (n = 35)
Systolic Blood Pressure (Mean (Standard Deviation))	147 (38)	112 (12)	154 (45)
Diastolic Blood Pressure (Mean (Standard Deviation))	92 (39)	88 (24)	95 (62)
BMI(Mean (Standard Deviation))	29 (6)	21 (7)	34 (12)
CRP (Median (Min – Max))	16.6*(0.30 – 42.6)	12.7*(3.4 – 15.2)	14.2 (8.54)
Urine Protein(Median (Min – Max))*	1 (0 – 3)	0 (0 – 3)	0 (0 – 3)

* Abnormal distribution, reported in median and minimum/maximum value.

DISCUSSION

Our study had not been used the newest terminology for severe preeclampsia according to ACOG 2013 which is preeclampsia with severe feature. According to subjects characteristics, most patients of severe preeclampsia patients were in second pregnancy with gestational age less than 37 weeks (preterm pregnancy). This is because every case of severe preeclampsia had to be terminated after stabilization, except for the gestational age less than 34 weeks that given lung maturation before terminated.^{1,2} Most patients came with very high blood pressure (median 182/100 mmHg) and obesity (mean BMI 30.51).

During study, we found that blood pressure still high until 2 years after delivery and also BMI still high in 6 months and 2 years after delivery. Those could be influenced by factors such as lifestyles, physical activity, cholesterolemia, and nutritional factors (eg. vitamin D). It is recommended that patients with history of preeclampsia in preterm pregnancy or with subsequent preeclampsia to have blood pressure, lipid profile, fasting blood glucose, and BMI examination every year, even though there is still limited evidence of accurate prediction of early onset preeclampsia to improve maternal and fetal outcome.^{1-3,21} Studies have shown that cardiovascular disease is increasing in first pregnancy with severe preeclampsia, with

higher risk rate compare to risk rate of pregnancy with subsequent severe preeclampsia, preterm labor, or intrauterine growth restriction, thus similar to risk rate of obesity or smokers.^{1,2,6} American Heart Association in 2019 is adding preeclampsia into one of the risk factors of short term and long term cardiovascular disease, and as a strong factor related to preterm labor.^{3,6,7}

Severe preeclampsia is mostly happening during preterm pregnancy and resulting outcome of growth and development not optimal for children that have been delivered. It can be caused by any factors, exacerbated by lack of awareness of how important to do antenatal care with health care provider and lack of education and supervision of health care provider to every pregnant patients, especially pregnant patients with high blood pressure. Most infants had been delivered in preterm condition (61.42%), resulting low birth weight babies and extreme low birth eight babies (the lowest baby weight in this study was 340 grams). Even though 77.17% infants were born alive, but only 63.78% had 5th-minute Apgar Score > 7. It is due to most infants born with weight < 2500 gram (75.59%). WHO study in 2014 found that 30.89% preeclampsia patients had preterm labors and 9% had perinatal mortalities, meanwhile 39.84% eclampsia patients had preterm labors and 22.66% had perinatal mortalities.²² During study, we found that 44.88% infants delivered are in healthy and normal growth – developmental state, 32.28% infants are still in below growth – developmental chart, and 22.84% infants are already died. Yet we still need to do further objective study of growth and development, especially infants with intrauterine growth restriction due to severe preeclampsia, eg. using Denver Charts, in collaboration with Social Pediatric Subdivision in Pediatric Department, measuring BMI and blood pressure, or vitamin D levels.²³⁻²⁵ One of example was using Peabody Picture Vocabulary Test-Revised (PPVT-R) to assess verbal ability and Raven's Colored Progressive Matrices (CPM) to assess non – verbal ability of 10 years old children delivered from preeclampsia patients.²³

Lots of studies of CRP had been done by cardiologists as measurement and marker of cardiovascular risks. CRP is a marker protein that sensitive to acute systemic inflammation, and considered related to cardiovascular risks in patients with history of preeclampsia.^{14,15} CRP levels were not increasing in patients with history of preeclampsia in their next pregnancy

and from 255 patients studied only 50 patients had subsequent preeclampsia with insignificant difference of CRP levels between both groups.¹⁸ From our study, we found that 6 months until 2 years after delivery are still high (>5mg/l), correspond to endothelial dysfunction in preeclampsia inducing inflammation process, thus increasing CRP level. We also concluded that preeclampsia are continuing disease causing complications, especially cardiovascular disease, and closed continuous observation to patients with history of preeclampsia are necessary. We also suggest to have further research with longer time of study groups and to learn changes in CRP levels that increased risk of subsequent preeclampsia in next pregnancy or cardiovascular diseases. From these further studies hopefully we may determine a baseline, specificity, and sensitivity of CRP levels for those risk factors. It will be one of consideration for these patients during antenatal care in her next pregnancy the needed to do CRP level measurement as early screening of preeclampsia and cardiovascular disease. Many factors may influence the increasing of CRP levels such as vitamin D levels, LDL levels, physical activities, lifestyles, and BMI. CRP levels are decreasing in patients with higher BMI but improvement of vitamin D levels and lifestyles, thus decreasing cardiovascular risks.^{14,22} This study to be continued by considering those factors influencing CRP levels in longer time of study.

There are changes of urine protein results before and after delivery in this study, correspond to endothelial dysfunction in severe preeclampsia that cause changes in blood vessels reactivity, loss of vascular integrity, and coagulation cascade activation.^{1-3,15} However in few studies, some HELLP syndromes and eclampsia cases had negative urine protein.^{9,26} Our study is using dipstick urine protein which is qualitative examination that depend on urinary concentration with high false positive and false negative values.^{1-3,9} We decided to use this tool because it is not expensive and not required certain skills.

The strength of our study is the numerous amounts and varieties of severe preeclampsia cases in Dr. Cipto Mangunkusumo NCGH supported with complete facilities, that this study could be done well in this education center. The weakness of our study are difficulties in gathering and contacting subjects due to lack of subjects' information in medical records (locations and

phone number) and their activities in time of study. Our study also did not have control group to be compared to, before and after delivery (clinically and laboratory), and between normal pregnancy and pregnancy with severe preeclampsia in the same time. Also we have limitations in performing laboratory examinations which influencing CRP levels, such as leucocytes, vitamin D, LDL levels, that we can not exclude sign of infection objectively and comprehensively. Thus this study could not determine the baseline, specificity, and sensitivity of CRP level as a marker for subsequent or worsening of severe preeclampsia in next pregnancy. We were using quantitative CRP examination in this study, furthermore we suggested to use hsCRP examination to have more specific results. This study were using descriptive cross sectional study design, so we were not able to have more accurate and systematic long term outcomes. Last condition of the babies delivered from the subjects were still subjectively and not specifically done, we suggested to use questionnaire about infants growth and development and factors influencing it, such as infant's BMI, growth and development pattern (eg. using Denver Charts), and infant nutritional status (eating habits, lifestyle, nutritional/diet measurements).

CONCLUSION

From this study we found that long term outcomes of blood pressure and BMI patients with history of severe preeclampsia are still high. CRP levels are also high even until 2 years after delivery, in contrary with urine protein had negative results in same time. Long – term outcomes of infants delivered from mother with history of severe preeclampsia are mostly in preterm labor condition and low birth weight, and less than 50% that have normal growth and developmental state until 24 months of age.

This study furthermore should be continued with prospective and analytical study that able to study and determine CRP levels before and after pregnancy, even before the next pregnancy, to compare CRP levels in normal pregnancy and pregnancy with severe preeclampsia, with considering factors influencing the increasing of CRP levels. Further study will have better quality if infants from the subjects are also join the study to be examined objectively, in collaboration with Social Pediatric Subdivision in Pediatric Department.

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