Maternal age ≥ 35 years, Nulliparity, High Blood COHb Levels, and Low Serum Nitric Oxide Levels Increased Risk of Preeclampsia

Ita Rahmawati[1], Anies[2], Mateus Sakundarno Adi[3], Cahyono Hadi[3]

[1]Doctoral Student, Faculty of Public Health, Diponegoro University, Semarang, Indonesia, [2]Professor, Faculty of Medicine, Diponegoro University, Semarang, Indonesia, [3]Associate Professor, Faculty of Public Health, Diponegoro University, Semarang, Indonesia

Abstract

Objective: To find out the risk factors for preeclampsia.

Materials and Methods: a case-control study was between March 2018 and December 2018. Pregnant women who with gestational age of at least 22 weeks live in residential areas, exposed to smoke from combustion of tile or brick were divided into two groups. Cases were those diagnosed with preeclampsia. Controls were normotensive pregnant women who had a history of preeclampsia in previous pregnancy. CO (carbon monoxide) exposure in pregnant women was determined by examining COHb levels in the blood. Serum Nitric Oxide levels were measured using the ELISA (*Enzyme-Linked Immunosorbent Assay*) method. Data were analyzed by Chi-square test or Fisher's exact test, Independent T-Test and regression analysis. Adjusted odds ratio (ORs) with 95% confidence interval (CI) was calculated.

Results: The results of Blood COHb levels were significantly higher in preeclampsia (4.58±1.2) than the case of control group (2.85±0.4). Serum nitric oxide levels in preeclampsia were significantly lower in preeclampsia (18.28±4.1) than the case of control group (35.15±7.2). Maternal age ≥ 35 years, nulliparity, high blood COHb levels > 3.5%, and low serum Nitric Oxide levels < 25 µmol/L were significantly associated with increased risk of preeclampsia.

Conclusion: Low serum Nitric Oxide levels (< 25 µmol/L) due to exposure to CO from the smoke of combustion of tiles or brick carried an increased risk of developing preeclampsia (ORs 25.5;95% CI 4.3-29.7). These results can help health workers in pregnancy care counseling and prevention of preeclampsia in pregnant women located in areas exposed to carbon monoxide from the smoke of combustion of tiles or brick.

Keywords: *Nitric oxide, Carbon monoxide exposure, Tiles-brick smoke burning, Preeclampsia.*

Introduction

Preeclampsia (PE) is the main cause of pregnancy and the development of 3-7% of pregnant women. Hypertension in pregnancy affects about 8% of pregnancies worldwide and significantly contributes to maternal and fetal morbidity and mortality.[1,2] The high number of maternal deaths in Indonesia, as compared to neighboring countries in other ASEAN regions dominated by hypertension in pregnancy or PE. Likewise, the cause of death in Jepara District was 85.7% due to preeclampsia, both of which occurred during pregnancy and postpartum.[3–5]

PE is a pregnancy-specific disorder that is defined as the new onset of maternal hypertension and proteinuria after 20 weeks of pregnancy.[6] Although until now there

Corresponding author:
Ita Rahmawati,
Doctoral Student, Faculty of Public Health, Diponegoro University, Semarang, Indonesia,
Email: rahma.safii@gmail.com

is no known exact cause of preeclampsia.[2,7]

PE is characterized by the migration of disturbed extravillous trophoblasts to the uterine spiral arteries which causes increased uteroplacental vascular resistance and vascular dysfunction, which results in reduced systemic vasodilation. Its pathogenesis is mediated by the bioavailability of biological Nitric Oxide (NO) and tissue damage caused by increased levels of Reactive Oxygen Species (ROS). Coagulopathy caused by ROS causes placental infarction and disrupts uteroplacental blood flow in PE. However, placental ischemia in PE reduces antioxidant activity, which results in increased oxidative pressure that causes the emergence of PE pathological conditions including hypertension and proteinuria.[6,8,9]

In developing countries, pollution exposure also comes from burning biomass fuels (wood, cow oil and plant waste). Combustion by products include carbon dioxide, carbon monoxide, nitrogen oxides, sulfur dioxide, and small solids and liter.[10] Carbon Monoxide (CO) is the pollutant that is most widely emitted from biomass combustion fumes that affect health. [11,12] Examination of COHb blood taken through venous blood vessels is the only biological monitoring method to determine the level of CO exposure in the body.[13] CO poisoning can increase Nitric Oxide (NO) activity and form free radical formation which stimulates leukocyte adhesion and activates the brain microvascular and then forms xanthine oxidase formation resulting in oxidative stress from radical superoxide (O2-). Oxidative stress in pregnant women can cause placental ischemia and interfere with uteroplacental blood flow, finally produces lipid peroxidation in PE.[14]

Materials and Method

a case-control study was carried out at Nalumsari Health Center, Mayong 2 Health Center, and Kalinyamatan Health Center, Jepara District between March 2018 and December 2018. Data from this study were collected from medical records of pregnant women at Nalumsari Health Center, Mayong 2 Health Center, and Kalinyamatan Health Center, Jepara District.

Pregnant women with gestational age of at least 22 weeks, who live in residential areas exposed to smoke from combustion of tile or brick (Nalumsari Health Center, Mayong 2 Health Center, and Kalinyamatan Health Center, Jepara District) dan were inclusion criteria. Subjects were divided into two groups. Cases were those diagnosed with preeclampsia. Controls were normotensive pregnant women who had a history of preeclampsia in previous pregnancy. Pregnancies complicated with chromosomal or structural anomalies, incomplete clinical data and not willing to be a respondent were excluded.

The medical records of pregnant women were reviewed. CO exposure in pregnant women was determined by examining COHb levels in the blood. In accordance with ACGIH (2008), Biological Exposure Indices or permissible COHb levels in the blood were 3.5%. [15] Nitric Oxide levels examined in this study were Nitric Oxide levels in the respondent's serum. Normal serum Nitric Oxide levels were 25-45 μmol/L.[16] Blood collection was carried out with the help of a Clinical Pathology Laboratory officer at the General Hospital of Kumalasiwi Kudus and then centrifuged on blood samples so that the Nitric Oxide serum was obtained for further analysis using the ELISA method while analyzed Blood COHb levels using spektofotometri.

Preeclampsia was defined as new-onset hypertension (systolic blood pressure of at least 140 mmHg; diastolic blood pressure of at least 90 mmHg), accompanied by proteinuria of at least 300 mg per 24 hours, or at least 1+ on dipstick testing after 20 weeks. [6,17]Gestational age [GA] was calculated from the last menstrual period and confirmed by first or second-trimester ultrasonography.

All data were analyzed with SPSS. Continuous variables were compared using Independent T-Test and presented as mean. The normality of data distribution is recorded by the Kolmogorov-Smirnov test. Categorical variables were analyzed with Chi-square test or Fisher's exact test as appropriated and presented as the percentage. Multivariate regression analysis was used to evaluate the association between preeclampsia and the various risk factors. The risk factors that produced a point estimate at a p-value of < 0.1 on the univariate analysis were entered into a multivariate regression analysis. Adjusted odds ratio (ORs) with 95% confidence interval (CI) was calculated. A p-value < 0.05 was considered statistically significant.

Results

The maternal and pregnancy demographics are shown in Table 1. The mean maternal age, and nulliparity proportion significantly higher in the preeclampsia group than in controls. However, gestational age at first

antenatal visit, family history of hypertension were not significantly different between the two groups.

Table 1. Demographic characteristic of both groups

Characteristics	Preeclampsia (n=32)	Control (n=32)	p-value
Maternal age (years), mean ± SD	32.18±5.3	30.25±5.6	0.011
Parity :	18 (56.25)	17 (53.12)	0.023
Nulliparity			
Multiparity	14 (43.75)	15 (46.87)	
Gestasional age at first ANC (Weeks), mean ± SD	12.18±1.3	10.25±1.6	0.052
Family history of hypertension	12 (31.25)	5 (68.75)	0.074

Values are given as mean ± SD; n: number; ANC = Antenatal care; BMI = Body Mass Index

Table 2 shows the comparison of Blood COHb and serum Nitric Oxide levels in preeclampsia than control groups. The results of Blood COHb and Serum Nitric Oxide levels between both groups were significant (p-value < 0,05). Blood COHb levels were significantly higher in preeclampsia. Blood COHb levels > 3.5% was found in 21 cases (66%) of preeclampsia. Serum nitric oxide levels were significantly higher in control groups. Serum nitric oxide levels in preeclampsia were low (18.28 μmol/L). There was no maternal death in the present study.

Table 2. Comparison of Blood COHb and Serum Nitric Oxide levels of both groups

	Preeclampsia (n=32)	Control (n=32)	*p*-value
Blood COHb levels (%)	4.58±1.2	2.85±0.4	0.023
Serum Nitric Oxide levels (μmol/L)	18.28±4.1	35.15±7.2	0.001

Values are given as mean ± SD; n: number

Table 3 provides the information regarding the risk factors in women with preeclampsia and controls through univariate analysis. Maternal age, parity, Blood COHb levels, and Serum Nitric Oxide levels were significantly associated with increased risk of preeclampsia.

Table 3. Risk factors for preeclampsia

Risk factors	Preeclampsia (n=32)	Control (n=32)	p-value
Maternal age (years) :	4 (12.50)	8 (25.00)	0.065
< 20			
20-34	17 (53.12)	14 (43.75)	Reference
≥35	11 (34.38)	10 (31.25)	0.021

Cont... **Table 3. Risk factors for preeclampsia**

Parity	18 (56.25)	17 (53.13)	0.023
Nulliparity			
Multiparity	14 (43.75)	15 (46.87)	Reference
Gestasional age at first ANC (Weeks) :	14 (43.75)	20 (62.50)	Reference
1-13			
14-26	6 (18.75)	9 (28.13)	0.120
≥27	12 (37.50)	3 (9.37)	0.200
Family history of hypertension :	20 (62.50)	27 (84.38)	Reference
No			
Yes	12 (37.50)	5 (15.62)	0.170
Blood COHb levels	21 (65.63)	17 (53.13)	0.004
High > 3.5%			
Low ≤ 3.5%	11 (34.38)	15 (46.87)	Reference
Serum Nitric Oxide levels	2 (6.20)	19 (59.38)	0.082
High > 45 µmol/L			
Normal 25-45 µmol/L	6 (18.75)	4 (12.50)	Reference
Low < 25 µmol/L	24 (75.00)	9 (28.12)	<0.001

Table 4 shows the results of multivariate logistic regression analysis. The risk factors that were significantly associated with increased risk of preeclampsia were: maternal age ≥ 35 years (odds ratio (ORs) 2.2;95% CI 1.3-3.4), nulliparity (odds ratio (ORs) 1.1;95% CI 0.8-2.1), high blood COHb levels > 3.5% (odds ratio (ORs) 1.7;95% CI 1.1-2.9), and low serum Nitric Oxide levels < 25 µmol/L (odds ratio (ORs) 25.5;95% CI 4.3-29.7) were significantly associated with increased risk of preeclampsia. On the other hand, maternal age < 20 years (odds ratio (ORs) 0.5;95% CI 0.3-0.9), and multiparity (odds ratio (ORs) 0.9;95% CI 0.6-1.7) were significant protective factors against the development of preeclampsia.

Table 4. Results of multivariate logistic regression analysis

Risk factors	**Adjusted ORs**	**95% CI**
Maternal Age ≥35	2.2	1.3, 3.4
Nulliparity	1.1	0.8, 2.1
High Blood COHb levels > 3.5%	1.7	1.1, 2.9
Low serum Nitric Oxide levels < 25 µmol/L	25.5	4.3, 29.7

Discussion

The results of blood COHb levels were significantly higher in preeclampsia than the case of control groups. Blood COHb levels > 3.5% was found in 24 cases (75 %) of preeclampsia. This is due to exposure to carbon monoxide from the smoke of combustion of tiles or brick (CO poisoning). Carbon Monoxide (CO) is the most pollutant emitted from biomass combustion fumes such as engine combustion, gas, oil, wood or coal-fired equipment, and solid waste disposal that affects health.[11,18] Meanwhile, CO poisoning can increase Nitric Oxide (NO) activity and form free radical formation, which stimulates leukocyte adhesion and activates the brain microvascular and then forms xanthine oxidase formation resulting in oxidative stress from radical superoxide (O2-). Oxidative stress in pregnant women can cause placental ischemia and interfere with uteroplacental blood flow, finally produces lipid peroxidation in PE.[14]

Serum nitric oxide levels were significantly lower in preeclampsia than the case control groups. Nitric oxide production has decreased in preeclampsia mothers associated with endothelial dysfunction so that it is thought to have an effect on vasoconstriction and hypertension in preeclampsia.[18] Its pathogenesis is mediated by the bioavailability of biological Nitric Oxide (NO) and tissue damage caused by increased levels of Reactive Oxygen Species (ROS). Coagulopathy caused by ROS causes placental infarction and disrupts uteroplacental blood flow in PE. However, placental ischemia in PE reduces antioxidant activity which results in increased oxidative pressure, that causes the emergence of PE pathological conditions including hypertension and proteinuria.[6,8,9]superoxide (O2-

Nulliparity and maternal age ≥ 35 years were associated with a significantly increased risk of preeclampsia. This was consistent with previous studies.[19–21] In both animal and human models, increased blood pressure has been associated with oxidative stress in blood vessels. Excessive endothelial production of reactive oxygen species (ROS) can be a cause and effect of hypertension. In addition to nitric oxide synthase can also be considered as a major source of Specific Reactive Oxygen (ROS), possibly contributing to the development of hypertension.[22] The authors found that blood COHb levels increase to cause a decrease in serum Nitric Oxide levels. Therefore, prevention of preeclampsia can be conducted by pregnant women by avoiding exposure of combustion.

The present study has mentionable limitations. First, this study was not reviewing other smoke exposures besides tile and brick smoke were not examined in this study such as smoke from motor vehicles and cigarette smoke. Second, the 6-month duration of the present study, may not have been long enough to elucidate the ling-term effects of this combustion.

Conclusion

The research results show blood COHb levels are significantly higher in preeclampsia than the case of control groups. However, serum Nitric Oxide levels are significantly lower in preeclampsia than control groups. Maternal age ≥ 35 years, nulliparity, high blood COHb levels > 3.5%, and low serum Nitric Oxide levels < 25 μmol/L were significantly associated with increased risk of preeclampsia. This study serves information about the roles of health workers as counselor to the prevention of preeclampsia especially pregnant women, which are located in areas exposed to carbon monoxide from the smoke of combustion of tiles or brick. Furthermore, prevention of PE by especially risk factors for exposure to carbon monoxide from tile and brick burning smoke should be encouraged to reduce the prevalence of PE. This role is very important in developing countries to cost efficiency.

What is already known on this topic?

Serum Nitric Oxide levels are significantly lower in preeclampsia. Low serum Nitric Oxide levels (< 25 μmol/L) due to exposure to carbon monoxide from the smoke of combustion of tiles or brick carried an increased risk of developing preeclampsia.

What does this study add?

This research has confirmed that blood COHb levels increase to cause a decrease in serum Nitric Oxide levels. Therefore, PE especially risk factors for exposure to carbon monoxide from tile and brick burning smoke can be prevented through reducing the intensity of carbon monoxide exposure.

Acknowledgment

Authors thank to the Directorate of Research and Community Service (DRPM) DIKTI, which have financed this program through the Lecturer Dissertation Research (PDD) grant program from 2018.

Potential Conflicts of Interest: None.

Ethical Clearance: The present study was approved by the Research Ethics Committee of the Faculty of Public Health Diponegoro University No.194/EC/FKM/2018.

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