Comparison-of-lc3-and-caspase-3-level-in-normal-pregnancy-early-onset-preeclampsia-and-late-onset-7458

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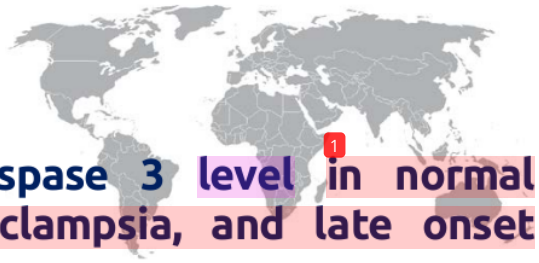

Comparison of LC3 and Caspase 3 level in normal pregnancy, early onset preeclampsia, and late onset preeclampsia

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ABSTRACT

Background: Preeclampsia is still become main cause of maternal and perinatal morbidity and mortality in addition to bleeding and infection. Preeclampsia is a pregnancy complication that occurs in about 5-10% and become main cause of maternal and fetal mortality and morbidity. The etiology and pathogenesis of preeclampsia syndrome have not fully understood. Autophagy and apoptosis is thought to play a role in the pathogenesis of preeclampsia. This research was done to see the difference in the expression of LC3 and Caspase 3 in normal pregnancy, early onset preeclampsia (EOP) and late onset preeclampsia (LOP) groups.

Methods: This was a cross sectional study, research was conducted in February until May 2014. Immunohistochemical examination of the placenta was done to assess the expression of LC3 and caspase 3.

Results: Expression of LC3 in EOP was higher than LOP and normal pregnancies expression of Caspase 3 in EOP was higher than LOP and normal pregnancy expression of Caspase 3 in EOP was higher than normal pregnancy.

Conclusions: There was no difference between expression of LC3 in normal pregnancy, EOP and LOP but there was a difference between expression of Caspase 3 in normal pregnancy, EOP and LOP. There was a difference between expression of Caspase 3 in normal pregnancy and LOP.

Keywords: LC3, Caspase 3, normal pregnancy, early preeclampsia, late preeclampsia

INTRODUCTION

Preeclampsia is still become main cause of maternal and perinatal morbidity and mortality in addition to bleeding and infection. Preeclampsia is a collection of symptoms or syndrome in pregnant women with a gestational age of 20 weeks with a sign above the main form of hypertension and proteinuria. Until now this condition is still an obstetrical problem that still can't be solved (1-3).

Maternal deaths associated with preeclampsia worldwide were estimated about 10-15% and affects approximately 5-7% of pregnant women. While in Indonesia, the incidence of preeclampsia was approximately 3-10%. In Dr Hasan Sadikin hospital in 2006-2008 there were about 542 cases of preeclampsia form 7,285 deliveries with maternal and perinatal mortality rate 0.3% and 0.21%, respectively. Preeclampsia also resulted in an increased risk of perinatal mortality and morbidity, including abruption placentae, fetal growth restriction and preterm (2-7,28).

The etiology of early-onset preeclampsia (EOP) begins with disturbances in the process of implantation of the placenta. This resulted in the disruption of remodelling of the spiral arteries resulting in ischemia and hypoxia of the placenta. While the etiology of late onset preeclampsia (LOP) associated with mothers who have predisposing factors such as diabetes mellitus, chronic hypertension, obesity, autoimmune disorders, etc. Most cases of preeclampsia occurred just before full term (after 34 weeks gestation), but approximately 5-20% of cases of preeclampsia occurs before 34 weeks gestation. Maternal and perinatal outcomes of early-onset preeclampsia were less favourable than the late onset preeclampsia (2,9,10).

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Table 1: *Subjects Characteristics*

Characteristics	Normal Pregnancy	LOP	EOP	p
Age (years)				
Mean (SD)	30.6 (4.7)	31.7 (7.5)	34.7 (6.3)	
Median	31	32.5	33	0.411
Minimun – maximum	22-37	22-43	28-45	
Parity				
Primigravida	6	5	2	0.113
Multigravida	2	3	6	
Body Mass Index (BMI)				
<19	0	0	1	
20 – 24	3	1	3	0.345
25 – 29	5	7	3	
30 - 34	0	0	1	

Villous trophoblast apoptosis in patients with preeclampsia was found to be higher than in patients with normal pregnancies. Excessive apoptosis in villous trophoblast may cause damage to the placenta and leads to fetal developmental disorders. Apoptosis can be detected with LC3 and Caspase 3 markers. An increase of those cell death markers are expected in patient with preeclampsia. Villous trophoblast has a mechanism to maintain homeostasis and maintaining of excessive apoptosis (11-14).

One of the mechanisms to defend excessive apoptosis is autophagy. Autophagy is a mechanism that plays a role in normal cell growth, development and homeostasis, as well as maintaining a balance between synthesis and subsequent recycling of cell products (15-19).

Apoptosis and autophagy formerly known as cell death type I and II. But now autophagy is known has an important role in survival of the cells and causes cell death. Autophagy is the intracellular degradation system that plays an important role in helping cells facing oxidative stress. Autophagy is increased in response to various forms of disturbance such as a lack of nutrients, hypoxia, oxidative stress, growth factors, amino acid deficiency and excessive free radicals (15-20).

Research on the effect of autophagy in placental implantation in preeclamptic patients is still rare.

What is the mechanism in the pathogenesis of preeclampsia associated with autophagy is not clear. How autophagy interacts with apoptosis in determining the life or death of villous trophoblast in the existence of stress have not widely studied. For this reason researchers were interested to conduct this study and it was expected to be useful for the development of science by contributing an understanding of the influence of autophagy and its interaction with apoptosis in the pathogenesis of preeclampsia. The aims of this study was to compare the level of LC3 and Caspase 3 in normal pregnancy, early-onset preeclampsia, and late-onset preeclampsia. Moreover, this study was performed to Examine whether LC3 in LOP was higher than EOP and normal pregnancy. And in the other hand this study also examines whether Caspase 3 expression was higher in EOP than in LOP and normal pregnancy. The results of this study was analyzed statistically by using Shapiro Wilk, ANOVA, and Chi Square.

MATERIALS AND METHODS

The Ethical Committee of the hospital approved this cross-sectional study. The samples were taken with consecutive sampling methods. Population of this study was all pregnant women who delivered in Obstetrics and Gynaecology Department that met inclusions and exclusions criteria and willing to participate by completing informed consent. Samples of their placenta were taken and examined after delivery. This study has been conducted from February to Mei, 2014, which included 24 women. The expression of LC3 and Caspase 3 was examined through placenta by immunohistochemistry methods. All data were collected in a computerized database and statistically analysed by SPSS 21.0 [SPSS Inc., Chicago, USA].

RESULTS

The results of this can be seen in **Table 1**.

Table 1 shows that mean of maternal age was 30.6 in normal pregnancy group, 31.7 in LOP and 34.7 in LOP group. **Table 1** also shows that primigravida was 6 (75.0%) in normal pregnancy group, 5 (62.5%) in LOP group and 2 (25.0%) in EOP group. Multigravida was 2 (25.0%) in normal pregnancy group, 3 (37.5%) in EOP group and 6 (75.0%) in LOP group.

Table 2: *Comparison of LC3 and Caspase 3 Hystoscore Between 2 Study Groups*

Groups	Caspase 3 Hystoscore		LC3 Hystoscore	
	Z_{M-W}	P	Z_{M-W}	P
EOP vs LOP	0.989	0.323	0.644	0.520
EOP vs Normal	1.677	0.047*	1.086	0.278
LOP vs Normal	0.409	0.682	0.107	0.914

ZM-W = Mann Whitney Test *) one party test

Body Mass Index (BMI) <19 in EOP group was 1 (12.5%). BMI 19-24 in normal pregnancy group was 3 (37.5%), 1 (12.5%) in LOP group, and 3 (37.5%) in EOP group. BMI 25-29 in normal pregnancy group was 5 (62.5%), 7 (87.5%) in LOP group, and 3 (37.5%) in LOP group. BMI 30-34 in EOP group was 1 (12.5%)

After the normality test, Shapiro Wilks test showed that maternal age data was in normal distribution. Furthermore, maternal age was tested statistically by ANOVA with p value >0.05. For categorical data such as parity and BMI, we used Chi Square test with p value >0.05. It shows that all three study groups were homogeneous, so that these groups feasible to be compared.

Table 2 shows the comparison of Caspase 3 hystoscore between LOP and normal pregnancy group after statistically tested with Mann-Whitney test. We obtained p = 0.682 (p> 0.05), which means not statistically significant, whereas between normal pregnancy group and EOP we obtained p value = 0.047 (p <0.05), which means statistically significant, and between groups EOP and LOP groups we obtained p value = 0.323 (p> 0.05), which means not statistically significant.

Table 2 also shows the comparison of LC3 hystoscore between LOP and normal pregnancy after statistically tested with the Mann-Whitney test, we obtained p = 0.914 (p >0.05), which means not statistically significant, between EOP and normal pregnancies groups we obtained p = 0.278 (p> 0.05), which means not statistically significant, and between EOP and LOP groups, we obtained p value = 0.520 (p> 0.05), which means not statistically significant.

DISCUSSION

Based on the analysis using Shapiro Wilks statistical tests on LC3 expression for the three groups of this study, we found that data was not normally distributed, then statistical test was done using Kruskal test. Based on the analysis using Kruskal test, we obtained p value 0.591 (p>0.05), which means not statistically significant. It shows that there is no difference between LC3 expressions between three groups of this study.

Although result of this present study was not statistically significant but clinically the average of LC3 hystoscore obtained support the ideas in previous reports. Mean of LC3 expression in EOP was higher than LOP and normal pregnancy.

Results of this study do not support results of previous research conducted by Oh et al. (25), they found that LC3 expression in placenta of preeclampsia patients increased compared with normal group. Oh et al. (25) also observed that LC3 expression in JEG-3 cell line were made by hypoxia, they also found that increase in the expressions of LC3 were not statistically significant with p = 0,15.

From Table 1 we can see that mean of maternal age was higher in EOP group which was 34.7, followed by 31.3 in LOP group and the smallest in the normal pregnancy group which was 30.6. Then we performed ANOVA statistical test and obtained p value of 0.411, which means that this difference was not statistically significant.

Risk of preeclampsia in extreme reproductive age increased. According to research conducted by Duckitt et al. (21) risk of preeclampsia in women aged ≥40 years 7 times greater in both primiparous or multiparous. While research conducted by Conde-Agudelo (22) showed that maternal age <20 years or >35 years was associated with an increased incidence of preeclampsia. In research conducted by Tan et al. (23) from 2,213 deliveries with preeclampsia, preeclampsia risk increased 1.6% at age <20 years and 16.4% at age ≥ 45 years. Age greatly affect pregnancy, appropriate age for pregnancy ranged from 20-35 years. In this age, female reproductive organs have evolved and function optimally. Preeclampsia is common in young and primiparous women; this was due to immunological mechanisms of paternal antigen exposure for the first time. And in women older age, this may be due to the increasing age of the possible emergence of a variety of risk of health problems such as high blood pressure, diabetes mellitus and other diseases.

Parity factors associated with an increased risk of incidence of preeclampsia. According to research conducted by Duckitt et al. (21) risk of preeclampsia was 3 times higher in primigravida. And in research conducted by Tan et al. (23) from 2,213 deliveries with preeclampsia, incidence of preeclampsia was highest in primigravida (4.2%) and lowest in the second parity (2.6%). Women with preeclampsia may experience alteration of immune system and this can inhibit trophoblast invasion in the spiral arteries. This may explain how preeclampsia is more common in women exposed to

paternal antigens for the first time (first pregnancy) or in multigravida women with a new partner. The loss of immune tolerance also explains why the interval between pregnancies is a risk factor for preeclampsia.

Body Mass Index BMI of 25-29 was found in 15 subjects, 7 (87.5%) in LOP group, 5 (62.5%) in normal pregnancy group and 3 (37.5%) in EOP group. BMI 19-24 was found in 7 subjects, 3 (37.5%) in normal pregnancy and EOP group and 1 (12.5%) in LOP group. BMI of <19 and BMI of 30-34 was found in 1 (12.5%) subjects, one in each normal pregnancy and EOP group. Using Chi square test we obtained p value 0.34 which means that this difference between 3 groups was not statistically significant.

The increase in BMI before pregnancy also increases the risk factor for preeclampsia. According Duckit et al. (21), in one cohort study they found women who had a BMI of >35 before pregnancy increases the risk of preeclampsia as much as 4 times. Risk of preeclampsia decrease in women with a BMI of < 20 before pregnancy. While research conducted by Aksornphusitaphong A et al. (24) family history of Diabetes mellitus, BMI oF ≥ 25 and weight gain of ≥ 0.5 kg per week is a risk factor of EOP and LOP. In this study we also found 1 subject with underweight and obese on EOP group, as we know nutritional factors are also thought to play a role in the pathogenesis of preeclampsia. Obese woman was at risk to have chronic diseases such as hypertension, diabetes mellitus, etc.

The weakness of this study was some confounding factors that were not considered in sampling might affect the validity of this study such as differences in gestational age in study groups.

In sample selections, infection factors such as premature rupture of membranes should also receive attention. According to a review by Cuervo et al. (26) autophagy plays an important role in the defence mechanism against infection alternative of viruses, parasites and bacteria. Nutritional factors also affect the immune system mechanisms of this alternative. But the exact mechanism is still not clear. In this study, we also did not pay attention to these factors in the sampling.

Nutritional factors also need to get more attention; review conducted by Singletary et al. (27) suggested that dietary factors can influence some cellular processes including autophagy. Change of nutrition and metabolism in pregnancy can also contribute on preeclampsia and related processes (29). Various components of foods, including vitamin D, selenium, curcumin, resveratrol and genistein can stimulate vacuolization in autophagy process. This was also not considered in sampling.

Another limitation was examination methods used in this study. The expression of LC3 and Caspase 3 was examined through placenta by immunohistochemistry methods, which this method had clinical variation for each subject.

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