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PRIMARY RESEARCH

Bodyweight and body length of foetus in endothelial dysfunction model pregnant mus musculus as preeclampsia induction which was given mild regular exercise

Meitria Syahadatina Noor^{1*}, Budi Santoso², Triawanti³, Widjiati⁴^{1,3} Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia² Faculty of Medicine, Airlangga University, Surabaya, East java, Indonesia⁴ Faculty of Veterinary, Airlangga University, Surabaya, Indonesia

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Abstract

Preeclampsia is condition with diastol blood pressure become ≥ 90 mmHg and proteinuria in gestation more than 20 weeks. Maternal mortality in Indonesia was caused by preeclampsia as the number 2 of causes. Preeclampsia is signed by endothelial dysfunction. Prevention of preeclampsia had not been developed yet. Exercise is activity which can induce endogen anti inflammation and antioxidant. So, it can be used to prevent the same process in preeclampsia. The goal of this research was analyzing the difference of bodyweight and body length endothelial dysfunction pregnant Mus musculus which was given mild regular exercise and without exercise. This research was true experimental with post test only with control group design, consisted of 2 steps. Step 1 to know the dose of anti QA2, and step 2 to know the effect of mild regular exercise to bodyweight and bodylength of foetus. Step 2 consisted of 4 groups (K1 for control normal pregnant, K2 for injected anti QA2 as endothelial dysfunction model pregnant, K3 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since early pregnant, K4 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since 1 week before pregnant). The number of Mus musculus were 6/group based on Federer formula. Determination of anti QA2 dose to induce endothelial dysfunction was done by using some doses and examining vasoconstriction of vessel in uterus by HE examanation. The dose that caused optimal vasoconstriction was 50 ng. The result showed there was no significant different of bodyweight among all groups ($p = 0.432$), but bodyweight in K4 (0.9102 grams) was more than K2 (0.8388 grams). There was no significant different of bodylength also among all of groups ($p = 0.662$), but bodylength in K4 (2.1897 cm) was longer than K2 (2.0939 cm). The conclusion was there was no significant differences of bodyweight and body length in endothelial dysfunction pregnant Mus musculus as preeclampsia induction which was given mild regular exercise and without exercise.

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I. INTRODUCTION

Preeclampsia Community Guidline (PRECOG) defined preeclampsia as condition with diastol blood pressure become more than 90 mmHg and proteinuria in gestation more than 20 weeks [1, 2]. Mechanism of preeclampsia related to oxidative stress, inflammation, and placentation [3, 4]. It causes endothelial dysfunction which is marked by decrease of vasodilatation, proinflammation, and prothrombine dysfunction [5, 6, 7, 8]. Preeclampsia model can

be made by making endothelial dysfunction with injection of anti QA2 (anti Human QA Lymphocyte Antigen 2 Region). It blocked placental QA2 expression. QA2 was homolog with Human Leucocyte Antigen-G (HLA-G) in human. Low expression of HLA-G in trophoblast was the predictor od endothelial dysfunction in preeclampsia [9]. Animal model which was injected by anti QA2 had higher urine protein than normal pregnant animal [10]. Effects of preeclampsia into foetus were low birth wieht, retardation of foetus

* corresponding author: Meitria Syahadatina Noor

† email: drmeitria@yahoo.com

growth, and intra uterine fetal death [11]. [12] stated that baby birth weight from preeclampsia mother was lower than not preeclampsia mother. Zuhriana in [12] stated that preeclampsia had risk to make low birth weight as 34%. One of the indicators that can evaluate foetus growth were bodyweight and bodylength.

Effective management for preeclampsia should be prevention since early pregnant. Preeclampsia preventions that ever suggested were bedrest, regular exercise, reducing salt consumption, antioxidant, diuretic, progesterone, Nitric Oxide (NO), calcium and aspirine [13]. Regular exercise could increase cardiorespiration function that could be suitable for hypertension such as preeclampsia [13]. Mild regular exercise was exercise with low intensity and burden. [14] stated that mild regular exercise or combination of regular exercise and antiinflammation therapy could decrease proinflammation. Proinflammation could induce endothelial dysfunction.

Mild regular exercise could induce production of interleukin 6 (IL6) that would induce interleukin 10 (IL10) [15]. It also increased endogen antioxidant [16]. Those mechanism could be the basic mechanism of prevent endothelial dysfunction in preeclampsia. the exercise could be given since before pregnant as primary prevention, and given in the early of pregnant as secondary prevention to reduce progressivity of preeclampsia mechanism. By reducing preeclampsia mechanism, its effect to foetus could be decrease also. Therefore, this research aimed to investigate the effect of mild regular exercise to bodyweight and bodylength in pregnant *Mus musculus* with anti QA2 injection as endothelial dysfunction model to induce preeclampsia.

II. LITERATURE REVIEW

Some effects of exercise related to preeclampsia were [3].

A. Placental Development

Exercise for mother was good for placental and foetus growth, to launch blood circulation, and to induce mild hypoxia to make citotrophoblast proliferation. Exercise also could increase Placental Growth Factor (PIGF) to develop placental. So, exercise balanced placental angiogenic to produce healthy foetus.

B. Oxidative Stress

Exercise stimulated antioxidant such as Glutathione peroxidase and superoxide dismutase to reduce oxidative stress. So, that process could decrease risk of preeclampsia.

C. Endothelial Function

Exercise induced the proliferation of endothelial cell, and NO sintase expression. NO sintase produced NO to give response to vasodilatation and endothelial function. Good endothelial function after exercise decreased blood pressure, so it could prevent preeclampsia.

D. Immune and Inflammation Reaction

Aerob exercise could reduce inflammation dan increase anti inflammation.

Preeclampsia research could be done in animal model by injecting anti QA2 to block placental QA2 expression to induce inflammation process as the basic mechanism of endothelial dysfunction to induce preeclampsia [9]. Research of [10] showed that animal model that was injected by anti QA2 had high proteinuria, urine creatinine, and urine albumin/creatinine ratio. Those conditions were similar to women in preeclampsia.

Another research that was similar to this research was about effect of mild regular exercise to foetus number in animal model. There was no significant different of foetus number in mild regular exercise and control, but descriptively if mild regular exercise was done 1 week before pregnant can increase foetus number compared with preeclampsia group without mild regular exercise [17]. The results of study about mild regular exercise and preeclampsia can be the solution of preeclampsia prevention.

III. RESEARCH MODEL

A. Step 1

The goal of first step was to confirm anti QA2 dose that could make endothelial dysfunction model in *Mus musculus*. This research used true experimental with post test only with control group design. This research used pregnant *Mus musculus*, 3/group. The groups of first step research were anti QA2 dose of 10 ng, 20 ng, 30 ng, 40 ng, 50 ng and 60 ng. All of female *Mus musculus* were injected by PMSG dan HCG to synchronize oestrus cycle, and after that the female was mated by the male 1:1. The next day, they were separated and the female *Mus musculus* with vaginal plug were used for the research. Vaginal plug showed as day 0 of pregnant. Group 1 was injected by anti QA2 of 10 ng (0,1 ml) intra peritoneal in the first day of pregnant, they were terminated in the second day of pregnant. Group 2 was injected by anti QA2 of 10 ng (0,1 ml) intraperitoneal in the first and second day of pregnant, and was terminated in the third day of pregnant. Group 3 was injected by anti QA2 of 10 ng (0,1 ml) intraperitoneal in the first, second, and third day of pregnant and terminated in the fourth day. Group 4

was injected by anti QA2 of 10 ng (0,1 ml) intra peritoneal in the first until fourth day of pregnant and terminated in the fifth day of pregnant. Group 5 was injected by anti QA2 of 10 ng (0,1 ml) intra peritoneal in the first until fifth day of pregnant, and terminated in the sixth day of pregnant. Group 6 was injected by anti QA2 of 10 ng (0,1 ml) intra peritoneal in the first until sixth day of pregnant, and terminated in the seventh day of pregnant. Uterine of *Mus musculus* in each group that was terminated was taken. All of the uterines were examined by histopathology examination with HE coloration to know percentage of vasoconstriction of vessels in uterine. Optimal vasoconstriction was in 50 ng dose of anti QA2, so it was used as dose for making endothelial dysfunction.

B. Step 2

The goal of step 2 research was to investigate bodyweight and bodylength because of mild regular exercise in endothelial dysfunction model pregnant *Mus musculus*. Design of this research was true experimental with post test only with control group design. This research used pregnant *Mus musculus*, the same procedure with step 1. The number of *Mus musculus* were 6/group. This research had 4 groups (K1 for control normal pregnant, K2 for injected anti QA2 as endothelial dysfunction model pregnant, K3 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since early pregnant, K4 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since 1 week before pregnant).

C. Protocol of Mild Regular Exercise

- The speed was 14 cm/second for 15 minutes
- The frequency was once in two days until day 14 of pregnant
- The treadmill was no angle
- Daptation of treadmill that was used: first of all, using speed of 7 cm/second for 1 minute, 11 cm/seconds for 2 minutes, 14 cm/seconds for 15 minutes.
- Before exercise, *Mus musculus* must be given food and drink first.

D. Examination of Bodyweight and Bodylength

After termination, abdomen of *Mus musculus* was dissected to get uterine, and the foetus was taken. Each foetus was cleaned first with physiological water. Foetus was weighed by digital scale twice and was calculated the mean in gram. Foetus was placed on micrometer paper. Top of head and base of the tail was signed, and after that two of those signs was measured in cm.

E. Statistic Analysis

All of data were analyzed by normality and homogeneity test. If they were in normal distribution and homogenous, data were analyzed by One Way Anova with 95% of significance level.

IV. DATA ANALYSIS

A. Step 1

The results of step 1 research was in Figure 1, 2, and 3.

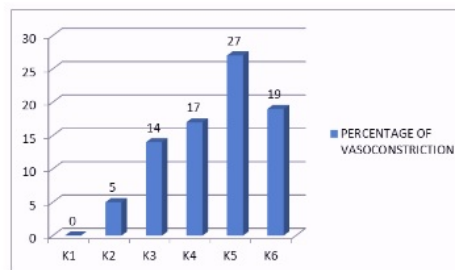


Fig. 1. Mean of uterine vessel vasoconstriction percentage

Note: K1 (anti QA2 10 ng), K2 (anti QA2 20 ng), K3 (anti QA2 30 ng), K4 (anti QA2 40 ng), K5 (anti QA2 50 ng), dan K6 (anti QA2 60 ng).

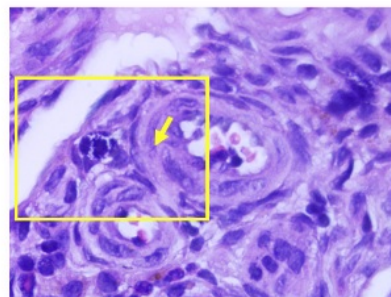


Fig. 2. Nucleus of myosin in normal arteriole wall (arrow). The shape was oval (uterine preparation; cross section; HE coloration; 1000x magnification; mikroskop Nikon H600L; camera DS Fi2 300 megapixel)

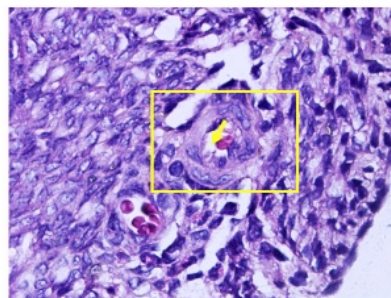


Fig. 3. Nucleus of myosin in vasoconstriction arteriole wall (arrow). The shape was notched (uterine preparation; cross section; HE coloration; 1000x magnification; mikroskop Nikon H600L; camera DS Fi2 300 megapixel)

Figure 1 showed optimal vasoconstriction percentage was in 50 ng dose. So, this research used 50 ng as the dose to make endothelial dysfunction to induce preeclampsia. anti QA2 injection was 10 ng perday intraperitoneal for 5 days. Activity of vessel constraction was signed by change of myosit nucleus structure in vessel wall. In normal condi-

tion, myosit nucleus was oval (Figure 2), but in constraction condition, myosit nucleus was notched (Figure 3).

B. Step 2

Step 2 research investigated bodyweight and bodylength of the groups. The results were in Table 1 and 2.

TABLE 1
ANALYSIS OF FOETUS BODYWEIGHT IN ALL OF GROUPS

Group	Mean of Foetus Bodyweight (Gram)	Deviation Standard	p Value	Statistic Analysis	Alpha Value
K1	0.6744	0.3882	0.432	One way Anova	0.05
K2	0.8388	0.4207			
K3	0.5979	0.3301			
K4	0.9102	0.2907			

Note: (K1 for control normal pregnant, K2 for injected anti QA2 as endothelial dysfunction model pregnant, K3 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since early pregnant, K4 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since 1 week before pregnant)

TABLE 2
ANALYSIS OF FOETUS BODYWEIGHT IN ALL OF GROUPS

Group	Mean of Foetus Bodyweight (Gram)	Deviation Standard	p Value	Statistic Analysis	Alpha Value
K1	1.9201	0.4314	0.662	One way Anova	0.05
K2	2.0939	0.4439			
K3	1.9367	0.4972			
K4	2.1897	0.3428			

Note: (K1 for control normal pregnant, K2 for injected anti QA2 as endothelial dysfunction model pregnant, K3 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since early pregnant, K4 for injected anti QA2 as endothelial dysfunction model pregnant with mild regular exercise since 1 week before pregnant)

All of data was in normal distribution and homogen, so analysis used One Way Anova with 95% significancy level. Table 1 showed there was no significant differences of foetus bodyweight between all of groups. Data in Table 2 also showed that there was no significant differences of foetus bodylength in all of groups.

V. DISCUSSION

A. Step 1

Figure 1 showed percentage of vessel vasoconstriction. The optimal vasoconstriction was in K5 (dose of 50 ng). This dose could block placental QA2 expression that started endothelial dysfunction to induce preeclampsia.

Every Mus musculus has QA2. It was a gen to protect body immunity, so natural killer cell recognized gestation as itself. If QA2 did not be expressed, natural killer cell recognized implantation as non self and induced mother's immune reaction. It recognized implantation as Damage Associated Molecular Patterns (DAMPs). This reaction continued become endothelial dysfunction to induce preeclampsia [9].

B. Step 2

Table 1 and 2 showed that foetus bodyweight and bodylength had no significant differences. This fact showed that mild regular exercise had not effected to foetus growth yet. Some factors that were indicated such as type of exercise in pregnant condition. [18] showed that the type of mild regular exercise that could effect to other's blood pressure in pregnant was aquarobic. It increased oxygen consumption. Its frequency was twice a week for 1 hour in the third trimester. If the blood pressure was stable, circulation to foetus was also stable and it could optimize foetus growth.

If the choice of regular exercise was still treadmill, so there must be continuing study that follow duration, angle of treadmill, and the time for starting exercise. It was similar to [19]. They said that there was no significant difference in intra uterine growth restriction. In that research, the factors that were included were glucose level, frequency, duration and intensity of the exercise.

Descriptive analysis of foetus bodyweight and bodylength in

Table 1 and 2 showed the different data. Mean of foetus bodyweight and bodylength in K4 (endothelial dysfunction model and given mild regular exercise since 1 week before gestation) were higher than K2 (endothelial dysfunction model by injecting anti QA2 without exercise).

From those descriptive data, the exercise 1 week before pregnant could be an early initiation for balancing process by producing antiinflammation and antioxidant. If the exercise was continued until pregnant, it was called as chronic effect of exercise. It gave positive effect to the body. Body produced IL10 as antiinflammation and endogen antioxidant after chronic exercise. It could reduce inflammation and oxidative stress in preeclampsia. because of that process, endothelial dysfunction also reduced. So the placentation became smoother. Smooth placentation made a good circulation for the foetus and its growth became better.

VI. CONCLUSION

The conclusion was there was no significant differences of bodyweight and body length in endothelial dysfunction

pregnant Mus musculus as preeclampsia induction which was given mild regular exercise and without exercise.

This research had limitations, because the research only examined physical anthropometric, and not confirmed yet with organ abnormality. Future direction of this research was finding the preventive solution for preeclampsia to reduce its complication and maternal mortality.

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