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PUBLISHER

Advanced Scientific Research

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PUBLICATION TYPE

Journals

ISSN

09752366

COVERAGE

2010-2021

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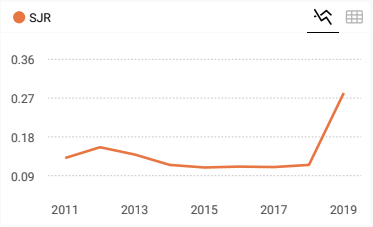

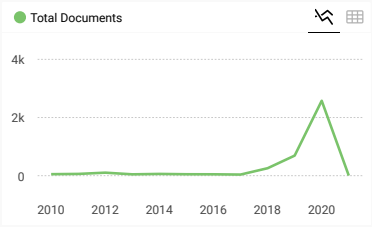

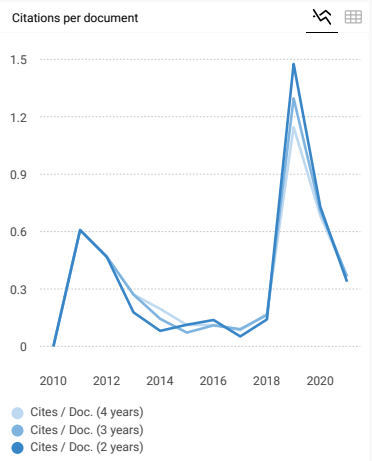

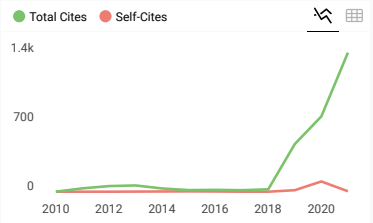

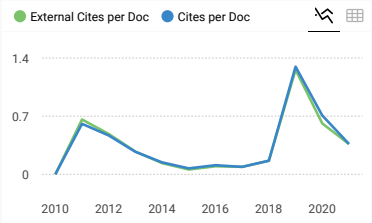

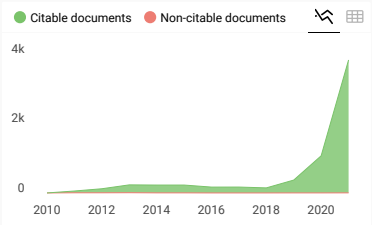

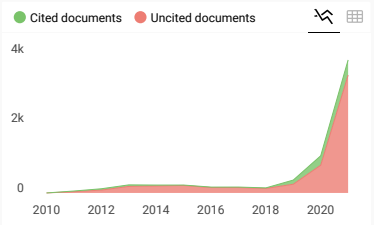

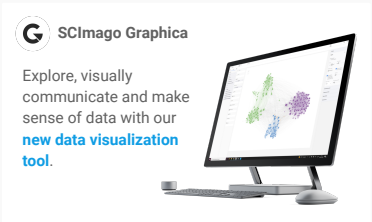

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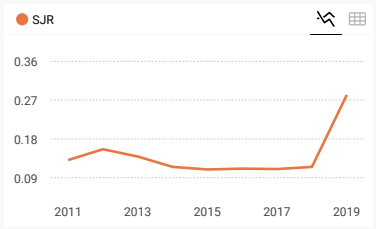

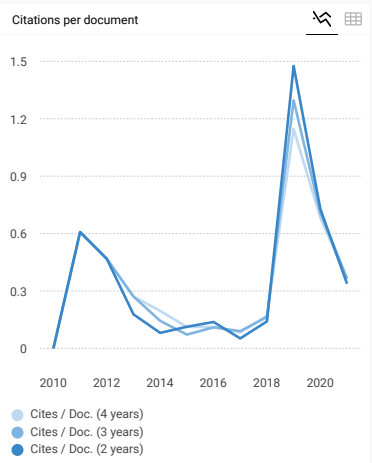

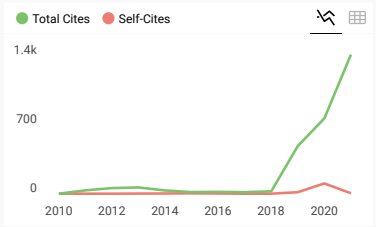

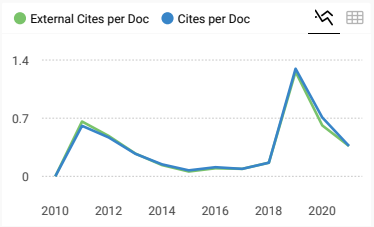

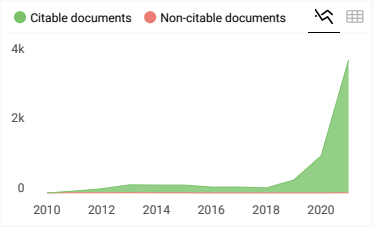

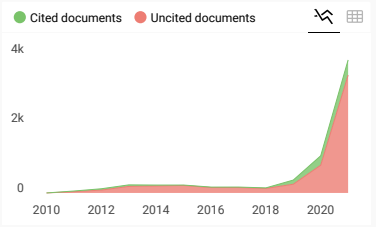

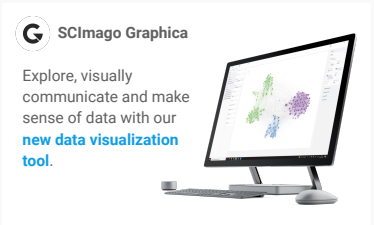

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ADITIAWARMAN , MANGGALA PASCA WARDHANA, DIANA APRILYANA NUR, HERMANTO TRI JOEWONO

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Research Article

The Effect of L-Arginine on Placental Growth Factor Serum Levels in Mouse Models with Preeclampsia

ADITIAWARMAN*, MANGGALA PASCA WARDHANA, DIANA APRILYANA NUR, HERMANTO TRI JOEWONO
Department of Obstetrics and Gynecology, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
*Corresponding Author
Email ID: *aditiawarman@fk.unair.ac.id
Received: 08.04.20, Revised: 22.05.20, Accepted: 13.06.20

ABSTRACT
L-Arginine has a role in the L-Arginine-nitric oxide pathway in preeclampsia, where in preeclampsia, it has been known to decrease the bioavailability of nitric oxide (NO). This study analyzed the effect of L-arginine on Placental Growth Factor (PlGF) levels in mouse models with preeclampsia. This study used a true experimental design with a randomized posttest-only control group. The sample of the study was Swiss *Mus musculus*, divided into three groups, namely normal pregnant mice, preeclampsia models without L-arginine and preeclampsia models with L-arginine. The mean serum of PlGF levels of the preeclampsia mouse models with L-Arginine was 962.431±158.211 pg/ml. This level was higher than the normal pregnant mice (947.339±208.267 pg/ml) and the preeclampsia mouse models without L-Arginine administration (861.985±161.960 pg/ml). There were no differences in PlGF levels between the group of normal pregnant mice and preeclampsia mice models without L-Arginine (p = 0.346). There were no significant differences between PlGF levels between the group of normal pregnant mice and the preeclampsia mouse models with L-Arginine (p = 0.865), and no significant differences were found between the groups of preeclampsia pregnant mouse models without and with L-Arginine administration (p = 0.202). Higher levels of PlGF were found in mouse models of preeclampsia with L-Arginine administration. However, there was no difference in PlGF levels between three groups.

Keywords: preeclampsia, L-arginine, PlGF.

INTRODUCTION

Preeclampsia is currently still providing maternal and perinatal morbidity and mortality, especially in developing countries. The prevalence of preeclampsia is around 5-15% of all pregnancies. In developing countries, preeclampsia is estimated to cause maternal deaths by 15-20%, acute and long-term morbidity in the mother, the risk of perinatal death, preterm labor, and stunted fetal growth (1–4). Preeclampsia is condition characterized by an increase in blood pressure accompanied by proteinuria (5). These complications increase in high-risk pregnant women, such as morbid obesity and vitamin D deficiency (6,7).

The imbalance of angiogenic and antiangiogenic factors is closely related to clinical signs and the severity of preeclampsia symptoms (8). Angiogenesis factors play a role in the implantation and placentation process that support the remodeling of spiral arteries and protect endothelial cells in the maternal vascular. Thus, uteroplacental circulation can take place properly (9). Placenta Growth Factor (PlGF) is one of the angiogenesis factors, part of Vascular Endothelial Growth Factor (VEGF), with a role in placental implantation and trophoblast growth. PlGF has a significant effect on the development of blood vessels and is mostly produced by the placenta. PlGF expression is dominated in the second trimester when there is an increase in uteroplacental circulation where remodeling of the spiral arteries is also starting now. Increased oxygen demand in the placenta causes invasion of the trophoblast, triggering an increase in PlGF expression. This increase in PlGF will trigger the proliferation of trophoblast cells (10). In addition, the PlGF level examination can be used as a predictor of early-onset preeclampsia (11).

Conversely, women who will experience preeclampsia will get a decrease in PlGF expression, interfering with trophoblast proliferation during the second half of pregnancy to cause disturbances of the spiral arteries remodeling and

further causing impaired placental implantation. This disorder contributes to hypoxia resulting in impaired fetal growth in patients with preeclampsia (10). In a hypoxic state, trophoblast cells will produce sFlt-1 with high amounts through the division of Flt-1 which will bind to VEGF and PlGF before being bound to receptors in the endothelium (Flt-1 and KDR) so that angiogenesis and vasculogenesis do not occur, inhibiting eNOS activation, inhibits endothelial cell migration, as well as triggering endothelial cell apoptosis (12).

L-Arginine has a role in the L-Arginine-nitric oxide pathway in preeclampsia. The impaired endothelial-dependent response has been reported in blood vessels isolated from women with preeclampsia. This indicates that endothelial nitric oxide (NO) production disruption can play an important role in mediating preeclampsia's pathophysiology. Several studies have shown that inhibition of NO production by specific inhibitors for NOS during pregnancy in mice will result in markedly increased arterial pressure, decreased GFR, proteinuria, IUGR, and slowing the increase in renal vasodilation in mid-gestation. The effects mediated by NO are reversible through the administration of L-Arginine. In addition, preeclampsia has been found to decrease the bioavailability of NO, possibly due to the accumulation of ADMA, an endogenous eNOS inhibitor, due to increased endothelial arginase activity (13). This study aimed to analyze the role of L-Arginine with changes in PlGF levels in pregnant mouse models with preeclampsia.

METHODS

This study used a true experimental design with a randomized post-test only control group. The research samples were 3-month-old *Mus musculus* Swiss strain, healthy, pregnant, weighing 20-30 grams, and had never been used as a trial animal for other studies. The samples in this study were 27, divided into three groups, namely normal pregnant mice, preeclampsia pregnant mice without L-arginine, and preeclampsia with pregnant mice with L-arginine in equal amounts. Preeclampsia pregnant mouse model obtained anti-Qa-2 10ng from day 1 to day 4, where anti-Qa-2 is anti-HLA-G, eliminating

HLA-G expression according to one of the pathogenesis pathways of preeclampsia. The preeclampsia pregnant mouse model group

received additional treatment in the form of L-Arginine as much as 200 mg/kgBW/day orally diluted with 1cc distilled water and then given per sonde on day 6 to day 14. On day 16, the termination was carried out in all groups (assumed to be a late second trimester of pregnancy in a human pregnancy where manifestations of preeclampsia occur in the second trimester and placentation has occurred well, and after the remodeling of the spiral arteries in the placenta, the mouse is completed). Serum PlGF levels were taken through blood in the intracardiac to be sufficient. The examination of serum PlGF levels was performed by the ELISA method. Ethical eligibility was obtained from the Research Ethics Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia.

The results of the study were analyzed statistically using the SPSS 20. The Shapiro Wilk normality test was performed to identify the data distribution. If the normal distribution was obtained, the differences between groups were analyzed using the continued test between the two groups with the Independent T-test if the normality test data obtained is a normal distribution, with an alternative using the Mann Whitney test. Probability is considered statistically significant if a p-value <0.05 is obtained with a confidence interval of 95%.

RESULTS

In this study, the mean serum PlGF level obtained by the preeclampsia model group with L-Arginine administration was 962.431 ± 158.211 pg/ml. This level was higher than the normal pregnant *Mus musculus* group (947.339 ± 208.267 pg/ml) and the preeclampsia *Mus musculus* model group without L-Arginine administration (861.985 ± 161.960 pg/ml). Table 1 shows the result of statistical analysis, there were no differences in PlGF levels between the group of normal pregnant mice and preeclampsia mice models without L-Arginine ($p = 0.346$). There were no significant differences between PlGF levels between the group of normal pregnant mice and the preeclampsia mouse models with L-Arginine ($p = 0.865$), and no significant differences were found between the groups of preeclampsia pregnant mouse models without and with L-Arginine administration ($p = 0.202$).

Table 1: Analysis of differences in PlGF levels between the groups

Groups	PlGF (pg/ml)	p
Normal pregnant mice	947.339 ± 208.267	0.346
Preeclampsia mouse models without L-Arginine	861.985±161.960	
Normal pregnant mice	947.339 ± 208.267	0.865
Preeclampsia mouse models with L-Arginine	962.431±158.211	
Preeclampsia mouse models without L-Arginine	861.985±161.960	0.202
Preeclampsia mouse models with L-Arginine	962.431±158.211	
Data are presented as mean±SD		

DISCUSSION

Serum PlGF levels in the preeclampsia *Mus musculus* group were lower than normal pregnant *Mus musculus*, and serum PlGF levels in the preeclampsia *Mus musculus* group with L-Arginine administration were higher than those in the preeclampsia *Mus musculus* without L-Arginine administration. When compared between the mean values of serum PlGF levels in the *Mus musculus* group of preeclampsia models with the administration of L-Arginine, the average results of serum PlGF levels that were higher than those of the normal serum levels of the normal pregnant mice group were obtained. The results are in accordance with previous study stating that in patients with preeclampsia, PlGF levels were lower than in normal women. A multicenter study conducted in the United Kingdom and Ireland in 2013 also stated that in 169 patients undergoing PlGF levels during 20-34/35 weeks' gestation, 73 patients with low PlGF levels had preeclampsia and only 3 patients with normal PlGF levels who have preeclampsia (14).

In this study, although there were differences in the mean between groups, the statistical test results did not show significant differences. This can be caused by several factors, including intracardiac blood sampling. PlGF levels assessed in this study were PlGF levels that were in the systemic. The levels of PlGF in this systemic cannot show the real condition because most of the PlGF is produced and obtained in the placenta. A journal states that PlGF is part of the VEGF family and is mostly expressed in the placenta, also in smaller amounts can be expressed in several other tissues, such as the heart, lungs, thyroid, liver, and skeletal muscle (10). The same research results obtained in other studies mentioning that PlGF, a group of growth factors, works locally, and the concentration in circulation cannot represent the amount of PlGF contained in uteroplacenta (15).

Also, preeclampsia is suspected as a result of placental dysfunction. One of the placental dysfunctions in patients with preeclampsia is triggered by immunological factors, namely the formation of AT1-AA (Angiotensin I autoantibody), which can activate the angiotensin aldosterone renin pathway, genetic factors through HLA-C mechanism, oxidative stress, and other factors such as decreased heme oxygenase expression. As a result, the placenta will produce antiangiogenic factors sFlt-1, sEng, and inflammatory mediators that will enter the maternal circulation and manifest in target organs of preeclampsia (16). Therefore, this study is expected to be the basis for further research on PlGF expression in the placenta to look deeper into the role of L-Arginine in the pathogenesis of preeclampsia through the PlGF pathway.

The factors include gestational age and the presence of anti-angiogenic factors affecting systemic PlGF levels, sFlt-1. Concentrations of PlGF in normal pregnant women are generally low in the first trimester of pregnancy and increase from weeks 11 to 12 and reach a peak at week 30, then decrease after that. PlGF expression in the placenta is dominated by the second trimester of pregnancy, coinciding with the angiogenesis of the fetoplacental blood vessels and maturation of the uteroplacental circulation. Placental growth factors can contribute to trophoblast invasion, increase trophoblast proliferation, and reduce apoptosis (10). As approaching the end of pregnancy, there is a reciprocal relationship between sFlt-1 and PlGF, with an increase in total sFlt-1 levels and a decrease in free PlGF levels. This shows that in the second half of pregnancy, low PlGF concentrations mainly occur due to the absorption of PlGF by sFlt-1. Low circulating PlGF may be a consequence of an abnormal initial occurrence in placentation and factors contributing to continuing abnormal growth during the second half of pregnancy. Decreased expression of PlGF can be caused by persistent

placental hypoxia due to uteroplacental undeveloped circulation (10).

Although the results of statistical tests were not significant, the differences in the mean PlGF levels in each group obtained in this study could be the basis of research to evaluate the effect of L-Arginine on PlGF expression on the placenta examined at the right time in preeclampsia mouse models. A clinical trial study on the efficacy of L-Arginine in preventing preeclampsia conducted on 100 pregnant women at risk of preeclampsia proves that the administration of L-Arginine 3g a day in pregnant women reduces the incidence of preeclampsia and the frequency of preeclampsia by 14.5%. The risk reduction in the group with L-Arginine was 26%, with an efficacy of 74%. Statistically, significant differences were found in reducing the incidence of severe preeclampsia. L-Arginine also reduces systolic, diastolic, and mean blood pressure. The results of this study also showed that L-Arginine prevents preeclampsia and increased blood pressure in patients at high risk of preeclampsia. Administering L-Arginine shows good results when given at 19-20 weeks of gestation. This L-Arginine therapy can be useful for patients at high risk of preeclampsia who arrive late at the first control (17). Some studies suggest that high doses of L-arginine supplements can improve blood vessel function (18–20).

This study evaluated the examination of PlGF levels after the action. Not knowing the initial PlGF levels before action is one of the limitations in this study because for the examination of PlGF levels, termination in animal models of preeclampsia must be carried out. In addition, this study also used animal models of preeclampsia, which certainly needs further evaluation if done in humans. Thus, confirmatory studies conducted in humans with proper methods will find out more of L-Arginine's effect in improving preeclampsia, one of which was shown by increasing PlGF levels. Although the results of statistical tests were not significant, the difference in mean PlGF levels in each group obtained in this study could be the basis of research to evaluate the effects of L-Arginine on the placenta through PlGF levels in preeclampsia.

CONCLUSION

PlGF levels were higher in preeclampsia mouse models with L-Arginine compared to the group of preeclampsia pregnant mouse models without L-Arginine administration. However, there was no difference in PlGF levels between the group of normal pregnant mice and those of the preeclampsia pregnant mouse models with L-Arginine administration.

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