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The Impact of Visfatin Level Against Blood Pressure Among Pregnant Women

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Abstract

Visfatin, a protein with a molecular weight of 52 kDa, has been demonstrated to increase in the bloodstream. Visfatin has been shown in several studies to be a potential marker of preeclampsia. The objective of this study was to describe visfatin levels in pregnant women in Gianyar, Bali. An observational design was employed in this study to describe visfatin levels in 41 pregnant women in Ubud, Gianyar regency, Bali. Visfatin levels were determined by examining EDTA blood samples using the Elisa method and reading them at 450 nm on a microplate reader. The average value of visfatin levels was 6.49 ng/ml, according to the results. The average visfatin level based on hypertension blood pressure respondents was 3.74 ng/ml. This result was lower than that of normal blood pressure respondents. This study's decrease in visfatin levels may have a smaller effect on physiological insulin resistance. The average visfatin level in second trimester respondents was 7.9 ng/ml higher than 5.7 ng/ml in third trimester respondents. The increase in visfatin levels suggests that visfatin may play a role in the pathogenesis of preeclampsia. Visfatin has the potential to be used as a biomarker to detect preeclampsia earlier, allowing pregnant women with preeclampsia to receive appropriate treatment.

Keywords: Preeclampsia, Pregnant Women, Visfatin.

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1. INTRODUCTION

Visfatin is a protein with a molecular weight of 52 kDa that is primarily discovered in visceral adipose tissue. This protein has 491 amino acids. Visfatin is also produced in the fetal, placental, and myometrium membranes (Fukuhara et al., 2005; Ihsan, Rini, & Yaswir, 2016; Marseglia et al., 2015). The visfatin/PBEF gene product was first identified as a lymphocyte-produced cytokine that promotes lymphocyte maturation and inhibits neutrophil apoptosis, hence the name pre-B-cell colony enhancing factor (PBEF). It was later discovered that nicotinamide phosphoribosyl transferase (Nampt), an intracellular form of visfatin, is a key enzyme in the biosynthesis of nicotinamide adenine dinucleotide (NAD) (Marseglia et al., 2015; Nourbakhsh et al., 2015).

Visfatin is insulin-mimetic and immunoregulatory. Visfatin has been associated with an increase in circulating blood levels in insulin-resistant conditions such as obesity, type II diabetes, and gestational diabetes (Ferreira et al., 2013; Hu et al., 2008). In pregnancies with preeclampsia, maternal circulating levels of visfatin are frequently elevated (Ferreira et al., 2013; Gorska et al., 2009).

Preeclampsia is a leading cause of maternal and fetal mortality and morbidity throughout the world. Preeclampsia is estimated to affect 2%-8% of all pregnancies worldwide, where the number of cases of hypertension caused by pregnancy (including preeclampsia) is on the rise and is the most common complication of pregnancy (ACOG Committee on Obstectric Practice, 2020). Although maternal mortality in patients with preeclampsia is very rare, the frequency of perinatal mortality is between 5%-14%. This figure escalates significantly when the patients have eclampsia (seizures). The frequency of complications that occur is associated with the gestational age at which preeclampsia began, the severity of the disease, and other medical problems (Leveno, 2018). Placental abruption, cerebrovascular injury, acute renal failure, pulmonary edema, and Hemolysis Elevated Liver Enzymes and Low Platelets (HELLP) syndrome are all examples of maternal morbidity. Preterm birth and intrauterine growth retardation (IUGR) are two short-term fetal consequences observed in nearly 25% of cases (Coban et al., 2020; Ukah et al. 2018).

In High blood pressure disorders account for 16% of maternal deaths in developing countries. In 2015, the maternal mortality rate during pregnancy, childbirth, and postpartum was 305 per 100,000 live births in Indonesia. In Indonesia, the leading causes of maternal death are bleeding, hypertension during pregnancy, and infection (ACOG Committee on Obstectric Practice, 2020; Kementerian Kesehatan Republik Indonesia, 2018). However, the etiology and pathophysiology is still unclear (ACOG Committee on Obstectric Practice, 2020. As a result, proper examination and treatment are required in cases of preeclampsia in pregnant women in order to prevent maternal mortality and childbirth

Visfatin may be a biologic marker of the metabolic syndrome in the context of preeclampsia, where circulating levels are identified to be elevated and placental disturbances occur. According to one study, visfatin levels in patients with preeclampsia were significantly higher in those with increased uterine artery impedance than in those with normal uteroplacental perfusion (Ferreira et al., 2013; Gorska et al., 2009).

The human placenta is now thought to be an active organ capable of secreting substances such as inflammatory cytokines and adipokines, which may contribute to insulin resistance. Furthermore, the placenta, a unique fetal organ during pregnancy, was found to express significant levels of visfatin in normal pregnancies (Ma et al., 2010). Visfatin is believed to have significance in the regulation of glucose balance. Type 2 diabetes, obesity, intrauterine growth retardation (IUGR), and gestational diabetes have a strong influence on its levels in blood plasma (Salan, 2017). Several studies have revealed that circulating of visfatin is

increased in pregnant women with IUGR and preeclampsia when compared to healthy pregnant women (Gorska et al., 2009).

Several studies have unveiled that visfatin possesses potential as a marker of preeclampsia. Hu et al., (2008) and Mazaki-Tovi et al., (2010) uncovered that visfatin levels in pregnant women decreased and were not much different from normal pregnant women (Hu et al., 2008; Mazaki-Tovi et al., 2010). Meanwhile, Fasshauer et al., (2008) revealed that visfatin levels were elevated in pregnant women with preeclampsia (Fasshauer et al., 2008).

Based on the 2018 Gianyar Health Agency Performance Report, the high maternal and infant mortality rates continue to be issues in carrying out activities in 2018 (Dinas Kesehatan Kabupaten Gianyar, 2020). Preeclampsia, as one of the leading causes of maternal death, necessitates the development of a widely applicable and affordable test that can diagnose asymptomatic preeclampsia and identify and monitor patients at risk. Thus, women and their children will receive the best prenatal care possible. A similar test would be useful for confirming a perplexing clinical diagnosis and for further research to determine prophylactic or temporary treatment. As a result, we selected Gianyar Regency as the research location for this study, specifically the Ubud sub-district. The objective of this study was to describe visfatin levels in pregnant women in Gianyar, Bali.

2.   RESEARCH METHOD

An observational design was used in this study to describe visfatin levels in pregnant women with preeclampsia in Ubud sub-district, Gianyar regency, Bali. The study was conducted in the Laboratory of the Medical Laboratory Technology Department of the Health Polytechnic of the Polytechnic Ministry of Health Denpasar from June to October 2022. This research has been approved by the code of ethics with the number LB.02.03/EA/KEPK/0082/2022 from health ethics committee of the Polytechnic of health Denpasar.

The number of samples in this study was 41 women, with inclusion criteria were pregnant women. Meanwhile, the exclusion criteria were pregnant women with special pregnancy conditions (ex: congenital disease, chronic disease, inflammatory treatment). We administered informed consent, which is a consent form as a respondent, to express pregnant women's willingness to participate in this study. The research interview sheet was used as a guideline for conducting interviews and recording respondents' interview results. Direct interviews with respondents were conducted to gather information about their identities and willingness to become respondents. Blood samples were obtained from respondents who agreed to the informed consent. A molecular analysis was performed on the blood sample. The blood examination results are processed as research data. Respondents who have agreed to the informed consent were taken blood samples. Plasma was collected using EDTA as an anticoagulant. Samples were centrifuged for 15 minutes at 2000-3000 rpm at 2-8^{0}C.

A total of 40μl of sample was added to the sample well and then 10μl of anti-Visfatin antibody was applied to the sample well, then 50μl of streptavidin-HRP was added to the sample well and wells. Mixed well. Apply sealer to the plate. Incubated at 37°C for 60 minutes. Then, washed it five times with a washing buffer. For each wash, the well is immersed in at least 0.35 ml of wash buffer for 30 seconds to 1 minute. All wells were aspirated and washed 5 times with wash buffer before being filled with wash buffer. The dish was dried on a paper towel or other absorbent material 50μl of substrate solution A was added to each well, then 50μl of substrate solution B was added to each well. The incubation plate was covered with a new sealer for 10 minutes at 37°C in the dark. Added 50μl Stop Solution to each well. Within 10 minutes of adding the stop solution, the optical density (OD value) of each well was

determined immediately using a microplate reader set to 450 nm. The data obtained were recorded, collected, processed, and presented in the form narratives, tables, and graphs.

3.   RESULTS AND DISCUSSION

This descriptive study with an observational design encompassed 41 pregnant women in the Ubud District, Gianyar Regency, Bali. The description of the characteristics of research subjects was based on age, gestational age, and blood pressure can be seen in Table 1.

Table 1. The Characteristics of Research Subjects.

Characteristics		Total
Age	20-30 years	24
	31-40 years	14
	41-50 years	3
Gestational Age	1-13 weeks	5
	14-27 weeks	18
	28-41 weeks	18
Blood Pressure	90/60 - 120/80 mm Hg	28
	121/81 – 139/89 mm Hg	12
	>140/90 mm Hg	1

The results of the examination of visfatin levels employing the Elisa method showed the average value of visfatin levels for 41 respondents was 6.49 ng/ml with the lowest level of 2.56 ng/ml and the highest level of 38.14 ng/ml. According to the findings of this study, the most age group of respondents was between the ages of 20 and 30. There were 18 respondents in the second trimester and 18 respondents in the third trimester among the 41 respondents. There are 28 people who have normal blood pressure.

Table 2. The Visfatin Levels Based on Blood Pressure.

Visfatin Levels (ng/ml)			Blood Pressure
Min	Max	Mean	Category
2.6	38.1	7.4	Normal
2.7	14.7	4.7	Pre-Hypertension
2.9	3.7	3.74	Hypertension

Based on the results obtained, the average visfatin level was classified into three categories based on the respondent's blood pressure, namely normal blood pressure, high blood pressure, and low blood pressure. (≤120/80 mm Hg), prehypertension (121/81 mm Hg – 139/89 mm Hg), and hypertension (≥ 140/90 mm Hg) (National High Blood Pressure Education Program 2004).

Table 3. The Visfatin Levels Based on Gestational Age.

Visfatin Levels (ng/ml)			Gestational Age
Min	Max	Mean	
2.8	6.8	4.2	First Trimester
2.6	38.1	7.9	Second Trimester
2.7	14.7	5.7	Third Trimester

The visfatin level based on the respondent's gestational age, which is categorized into the first trimester (1-13 weeks), second (14-27 weeks), and third (28-41 weeks).

Visfatin is an adipokine produced by visceral tissue, but it is also expressed in the placenta and fetal membranes during pregnancy. Visfatin is insulin-mimetic and immunoregulatory. Visfatin levels in the blood have been identified as being elevated in

insulin-resistant states such as obesity, type II diabetes, and gestational diabetes (Ferreira et al. 2013; Hu et al., 2008). According to Kar, (2014) and Salan, (2017) visfatin is one of the biomarkers of preeclampsia markers. Visfatin is an adipokine secreted by adipose tissue that plays a signifcant role in the biosynthesis of nicotinamide adenine nucleotide by catalyzing the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate to produce nicotinamide mononucleotide. Visfatin is also involved in the regulation of glucose homeostasis. Changes in plasma levels have been associated with a number of disorders, including type 2 diabetes mellitus, obesity, fetal growth retardation, and gestational diabetes mellitus. Visfatin levels are also related to the severity of preeclampsia (Fasshauer et al., 2007; Kar, 2014; Salan 2017).

Preeclampsia is a common pregnancy condition characterized by edema, hypertension, and proteinuria that occurs after 28 weeks of gestation and has an unknown cause. Early preeclampsia develops between 20 and 34 weeks of gestation, while late preeclampsia develops at or after 34 weeks (Dhariwal & Lynde 2017). Preeclampsia was discovered to be a direct threat to health from hypertension, which also increased cardiovascular disorders during pregnancy and was linked to an increase in cardiovascular disease later in life. Furthermore, it is a major cause of maternal and fetal mortality and morbidity (Shaheen et al. 2016). Predicting whether or not a pregnancy will result in preeclampsia is critical to ensuring that pregnant women receive the best care possible. There is currently no preventive therapy, thus, predicting the risk of preeclampsia should lead to more optimal treatment of patient hypertension development and reduce the severity of the disease (Dhariwal & Lynde, 2017).

There has been no consistent use of a therapy to prevent the development of preeclampsia. This is most likely due to the fact that the pathogenesis of the disease occurs several weeks before the patient develops symptoms. The majority of treatment aims to reduce the effects of inflammation, which manifests in later disease (Dhariwal & Lynde, 2017). Aspirin is the only therapy that has been shown to reduce the risk of preeclampsia in high-risk women. If given before 16 weeks of gestation, aspirin is effective in lowering the risk of preeclampsia (Fox et al., 2019). Low-dose aspirin has been proposed as a therapy to reduce the occurrence of preeclampsia. Endothelial dysfunction and the resulting activation of the platelet and clotting system are thought to be crucial aspects of preeclampsia symptoms. Aspirin is thought to reduce the frequency and severity of preeclampsia by inhibiting thromboxane formation Dhariwal & Lynde, 2017). Low-dose aspirin has been demonstrated to be beneficial in pregnant women at moderate to high risk, reducing the incidence of preeclampsia by about 15% (Askie et al., 2007; English, Kenny, & McCarthy, 2015).

One of the factors influencing the presence or absence of potential obstetric emergencies is age. Age is a risk factor for severe preeclampsia as well. Preeclampsia is said to be more prevalent in mothers over the age of 40. Adeline, Laksana, and Atika, (2018) discovered severe preeclampsia in the 17-34 age group out of 175 (73%) cases in their study (Adeline, Laksana, & Atika, 2018). Other research has demonstrated that being over 40 years old increases the risk of preeclampsia. Women over the age of 40, women with a history of preeclampsia, obesity before pregnancy, and women with donor eggs, donor embryos, or donor insemination all increase the risk of preeclampsia. Diabetes, pre-existing hypertension, and a family history of preeclampsia are all risk factors. Furthermore, various paternal factors can increase the risk of a preeclamptic pregnancy (English, Kenny, & McCarthy, 2015). This difference is probably due to the general age of mothers who experience pregnancy and childbirth at the age of 17 to 34 years, hence, the number of severe preeclampsia is also most generally discovered at that age (Adeline, Laksana, & Atika, 2018).

Visfatin levels were discovered to be lower in this study when compared to respondents with normal blood pressure. Visfatin levels decreased in respondents in the third trimester when

compared to respondents in the second trimester. These results are consistent with Hu et al., research's, (2008). Hu et al., (2008) discovered that visfatin levels in pregnant women with preeclampsia were lower than controls for pregnant women without preeclampsia and women who were not pregnant in their study. Visfatin levels in the third trimester were lower than in non-pregnant women and healthy pregnant women. Altered patterns of visfatin and other adipokines such as leptin, resistin, and adiponectin are identified to escalate insulin resistance during pregnancy and participate in the formation of physiological insulin resistance and are involved in the regulation of energy metabolism. Changes that occur at visfatin levels in this study possess a smaller effect on physiological insulin resistance (Hu et al. 2008).

In this study, the increase in visfatin levels occurred during the second trimester. Visfatin levels increased during PE beginning in the first trimester, indicating a possible role for visfatin in the pathogenesis of PE. Visfatin is abundantly expressed in adipose tissue, as well as the placenta and fetal membranes. Mean visfatin concentrations have been reported to be higher in the second and third trimesters of normal pregnancy than in the first, supporting the theory that visfatin is produced by the placenta and fetal membranes. Thus, it is possible that normal visfatin production is regulated to support fetal growth, but in PE, visfatin's supporting role is disrupted, resulting in PE (Amiri-Dashatan et al., 2020; Mastorakos et al., 2007; Ngala et al., 2016).

Fasshauer et al., (2008) discovered that serum visfatin levels in PE patients were significantly higher than in controls. According to Fasshauer et al., (2008), visfatin levels increased 1.4-fold in women with gestational diabetes mellitus when compared to controls of the same gestational age. Furthermore, visfatin levels in third trimester patients with intrauterine growth restriction (IUR) were identified to be doubled when compared to healthy pregnant women (Fasshauer et al., 2008). Increased levels of visfatin in pregnant women with PE were also revealed by Ferreira et al., (2013), Ngala et al., (2016), and Saheen et al., (2016) (Ferreira et al., 2013; Ngala et al. 2016; Shaheen et al. 2016).

To determine normal levels of visfatin in pregnant women, the potential of visfatin as a PE marker requires to be investigated further using a larger sample size. Such studies may even provide useful information on predicting the condition of pregnant women with PE, which could aid in the development of intervention programs to reduce the effects of PE on maternal and fetal morbidity and mortality, as well as the prevalence of stunting (Dewi et al., 2022).

Ngala et al., (2016) discovered that obese women are more likely to develop PE during pregnancy. This risk multiplies by two to three. The findings of this study show that a higher BMI (>28.8 kg/m2) has a high accuracy in predicting pregnancies that are likely to develop into PE. This suggests that excessive fat accumulation in the body plays a significant role in the pathogenesis of PE (Ngala et al. 2016).

Variations in study findings can be attributed to a variety of factors, including disease severity, metabolic disorders, blood sampling timing, serum or plasma from the blood, and the study's subject. Increased levels of visfatin have been connected to the pathogenesis of PE (Shaheen et al., 2016). Visfatin levels in PE may be higher than in the control group. This suggests that visfatin levels in the placenta are essential as evidence for success in predicting PE. More research is needed, however, to investigate these medical complications during pregnancy.

4. CONCLUSION

In accordance with the research results, visfatin levels in pregnant women with pre-hypertension and hypertension have lower levels than pregnant women with normal blood pressure. Visfatin levels increased in the second trimester compared to the first and third trimesters. Visfatin has the potential to be employed as a biomarker to detect preeclampsia, allowing pregnant women with the condition to be identified early. It is recommended that

future research be conducted with a larger number of samples. And it is recommended to use controls for healthy pregnant women and non-pregnant women.

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