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Article

DIFFERENCES OF HOMEOSTASIS MODEL ASSESMENT-INSULIN RESISTANCE (HOMA-IR) LEVELS BETWEEN OBESITY PREGNANT WOMEN WITH THE NORMAL WEIGHT IN PREECLAMSIA

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A B S T R A C T

Preeclampsia is a leading cause of maternal death. Maternal factors are the originators of late onset preeclampsia (LOP). One maternal factor is HOMA-IR that is associated with inflammation and insulin resistance. This study aims to determine differences in the mean maternal HOMA-IR levels between obese pregnant women and those who have normal weight in the Late Onset Preeclampsia.This study design is Comparative cross sectional, the study was conducted at Dr. M. Djamil Hospital, The Biochemistry Laboratory and the Biomedical Laboratory of the Faculty of Medicine, Andalas University, Padang in February 2016 - January 2017. The number of samples was 40 selected by consecutive sampling, which were divided into 2 groups: 20 obese respondents and 20 normal weight respondents. Resistin levels were examined by the ELISA method, then data were analyzed by the mann-whitney test.The results of the study showed that the median HOMA-IR level in the obese group was 1,291 (0,409 – 17,308) µU/ml dan mmol/L and the median normal weight group was 0,139 (0,004 – 0,370) µU/ml dan mmol/L. Statistically obtained p value <0.001 means that there is a significant difference between levels of HOMA-IR in obesity and normal weight. In conclusion, the median level of HOMA-IR was higher in the obese group than in the normal weight group. There is a significant difference between HOMA-IR levels in obesity and normal weight

I. INTRODUCTION

Preeclampsia is a major complication in pregnancy and a major cause of maternal and fetal morbidity and mortality. The World Health Organization (WHO) reports 16% of deaths caused by preeclampsia in developing countries. The incidence of preeclampsia ranges between 5-10% of all pregnancies [1]

The maternal mortality rate in developing countries caused by Preeclampsia is higher at around 5-10% and the fetal mortality rate around 40%. The maternal mortality rate due to hypertension in pregnancy in 2010 in Indonesia is more than 30% and the incidence of PE ranges from 3-10% .[2]

Preeclampsia is still a disease of theory. Various studies have not been able to explain clearly the exact cause. Theories that are widely adopted are: (1) The theory of placental vascularization abnormalities; (2) Theories of placental ischemia, free radicals and endothelial dysfunction; (3) The theory of immunologic intolerance between mother and fetus; (4) Cardiovascular adaptation theory; (5) Nutritional deficiency theory; (6) Inflammation theory.[3,4]

Analysis of preeclampsia risk factors is needed to reduce the adverse effects of preeclampsia. The risk factors are classified into 3 namely intrinsic factors and extrinsic factors which are the originators of Early Onset Preeclampsia (EOP) while maternal factors are the originators of Late Onset Preeclampsia (LOP). One maternal factor is HOMA-IR which is associated with inflammation and insulin resistance.[5,6]

Increased serum resistin levels are associated with a systemic inflammatory response and insulin resistance both of which are increased in preeclampsia compared to normal pregnancy. Yusrawati (2015) reported that the average Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) was higher in the group of Early Onset Preeclampsia (PEAL) than the Early Onset Preeclampsia (PEAD) group. [7,8,9,10]

Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) can be used as an indicator of insulin resistance, but not for inflammatory conditions, otherwise hs-CRP can be used as an indicator of inflammation, but not for insulin resistance. Resistin is thought to describe these two conditions, because it is associated with insulin resistance and inflammation. [11]

HOMA-IR is a maternal factor whose role is still being debated in pre-classification. Therefore the authors would like to conduct research on differences in the mean maternal HOMA-IR levels between Pregnant Women History of Obesity and Normal Body Weight in Late Pre-Severe Preeclampsia

This study aims to determine the differences in the mean maternal HOMA-IR levels between obese pregnant women and those who are of normal weight in the Late Onset Preeclampsia.

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II. METHODS

This research was conducted in the delivery room of RSUP. Dr. M. Djamil Hospital, the Laboratory of Biochemstry and the Laboratory of Molecular Biology, Faculty of Medicine, Andalas University Padang for one year starting in February 2016. This study is a comparative analytic study of two unpaired groups with a cross sectional approach to analyze the average levels of HOMA-IR of obese pregnant women. with those who have normal body weight on slow onset preeclampsia. The population in this study were all obese pregnant women and those of normal weight with gestational age> 34 weeks with a diagnosis of Severe Preeclampsia who were hospitalized in the maternity ward of the Dr. M. Djamil Hospital with 40 samples. Sampling was carried out using consecutive sampling techniques. Fasting blood samples were taken in the vein mediana cubiti after the sample fasted for 6-8 hours as much as 3 cc conducted by officers (nurses / midwives) who were on duty at the time of the study and approximately 2 hours of blood had been taken to the laboratory for centrifuge then inserted into the centrifuge tube (vacutainer) by means of the syringe handle allowed to bleed by itself from the syringe tube. The blood in the vacutainer is placed on a tube rack to avoid shaking and remain in position, then allowed to stand for 15-20 minutes. Blood was centrifuged at a rate of 2000-3000 rotations per minute (rpm) for 15-20 minutes at the Laboratory Biomedical Faculty of Medicine, Andalas University. Taking serum from the centrifuge results using a micro pipette, then the serum obtained is entered into a micro tube that has been coded according to the respondent's identity. Serum samples were immediately sent to the Laboratory Biomedical to be stored in a refrigerator with a temperature of -80ºC (can last 6 months), meanwhile for blood glucose measurements carried out at the Bio-Chemistry Laboratory Faculty of Medicine, Andalas University

After all samples are met, then measured according to the kit procedure used in the laboratory. HOMA-IR index is calculated by checking fasting glucose and insulin levels and then divided by a constant 22.5. The figure 22.5 is obtained assuming the calculation of normal fasting insulin level 5 µU / mL multiplied by the normal glucose level of 4.5 mmol / L, the result is 22.5. This study has received ethical approval from the Research Ethics Committee at the Andalas University School of Medicine. The HOMA-IR data obtained were analyzed by an unpaired T test.[12]

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III. RESULT

Table 1.1 Characteristics of Research Subjects Between Obese Pregnant Women and Those with Normal Body Weight Based on Mother's Age and Gravida

Variable	Grups						Total (%)	P Value
	Obese Pregnant			Normal Body Weight				
	n (%)	Mean±SD	Median (Min-Max)	N	Mean±SD	Median (Min-Max)		
Mother's age (year)	20	33,00 ±7,497		20	31,90 ± 6,719			0,628
Gravida group								
Primigravida	6 (15)			7 (17,5)			13(32,5)	
Multigravida	14 (35)			13 (32,5)			27 (67,5)	
Sumary	20 (100)			20 (100)			40 (100)	
Weight gain (KG)	20	13,15 ±4,902		20	13,00 ± 2,513			0,904
Sistole Blood Presure (mmHg)			170 (150 – 260)			170 (160 – 200)		0,899
Diastole Blood Presure (mmHg)			110 (90 – 160)			110 (100 – 140)		0,906
Leukocyte level (sel/mm3)			13,20 (7,00 – 15,93)			12,86 (8,10 – 15,96)		0,534

Based on table 1.1, it can be seen that the mean age in the obese group is 33.00 + 7.497, higher than in the normal weight group 31.90 + 6.719 years, statistically there is no difference between the two groups.

The distribution of parity in the primigravida and multigravida obese groups was 6 people (15%) and 14 people (35%), respectively. In the normal weight group, the distribution of primigravida and multigravida parity of 7 people (17.5%) and 13 people (32.5%), statistically showed no significant difference between the two groups.

The mean weight gain in the obese group 13.15 + 4.902 was almost the same in the normal weight group 13.00 + 2.513 kg, statistically showing no difference between the two groups.

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The median systolic blood pressure in the obese group was 170 (150-260) mmHg almost the same as the median normal weight group was 170 (160-200) mmHg. Statistically there were no significant differences between the two groups.

The median diastolic blood pressure in the obese group was 110 (90-160) mmHg almost the same as the median normal weight group was 110 (100-140) mmHg. Statistically there were no significant differences between the two groups.

The median leukocyte level in the obese group was 13.20 (7.00 -15.93) cells / mm3 higher than the median normal weight group was 12.86 (8.10-15.96) cells / mm3. Statistically there were no significant differences between the two groups.

To find out the difference in average HOMA-IR levels between 2 different groups, an unpaired t test was performed. HOMA-IR levels for each group of research subjects can be seen in the following table 1.2:

Table 1.2 Average HOMA-IR levels between 2 different groups

Variabel	Grups		P value
	Late onset preeclampsia with obesity N= 20 Median (min-max)	Late onset preeclampsia with normal body weight N=20 Median (min-max)	
HOMA-IR Levels (µU/ml and mmol/L)	1,291 (0,409 – 17,308)	0,139 (0,004 – 0,370)	0,000*

(*there is significant differences)

Based on table 1.2, it can be seen that for the historical obesity group in the Late onset preeclampsia (LOP), there is a significant difference in the average HOMA-IR levels with normal body weight.

IV. DISCUSSION

In this study, insulin resistance (IR) with a mean indicator of Homeostasis Assessment-Insulin Resistance model (HOMA-IR) was higher in the LOP group with a history of obesity compared to the LOP group with Normal Body Weight of 1.29 (0.409 - 17.308) vs 0.139 (0.004 - 0.00 0.370) with p = 0,000. Statistical tests showed a p value <0.005, indicating that the mean maternal serum HOMA-IR levels in LOP with a history of obesity were significantly higher compared to LOP with normal weight.

It is clear that IR plays a greater role in the LOP group with a history of obesity than in the normal weight LOP group, this is supported by Yusrawati's research which shows that HOMA-

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IR is higher in the LOP group than in the EOP (Early Onset Preeclamsia). This shows that IR has occurred before the failure of trophoblast invasion which is seen from the uterine artery dystolic notch which persists until 20 weeks' gestation. It was found in this study that the persistence of uterine artery notches was not only caused by intrinsic placental factors but could also be caused by IR factors that had occurred before the trophoblast invasion (Yusrawati, 2015)

Insulin plays a role in Preeclamsia through the insulin resistance pathway which causes free radicals. Free radicals can induce cell dysfunction which is the main pathophysiology of preeclampsia. Changes in endothelial function that occur are considered as the main causes of PE symptoms such as hypertension, proteinuria and activation of the hemostasis system (El-Refai AA et al. 2014)

One way to measure insulin sensitivity is the HOMA-IR formula. The results obtained by measuring fasting blood sugar levels and fasting insulin levels, because the units are not the same then to get the HOMA-IR value by fasting blood sugar levels multiplied by fasting insulin, the results obtained are converted into units of μU / L, then divided by 22 .5 (Singh and Saxena, 2010)

Insulin increases total blood flow and blood volume in skeletal muscle. The vasodilator effect of insulin is caused by an increase in NO production in the vascular endothelium via the eNOS pathway using a phosphorylation-dependent mechanism. Insulin requires the activation of insulin receptor tyrosine kinase to phosphorylate insulin substrate-1 receptor (IRS-1), causing the binding and activation of phosphatidylinositol 3-kinase (PI3K). This is followed by activation of 3-phosphoinositide-dependent protein kinase-1 (PDK-1) which will phosphorylate and activate Akt, which directly phosphorylates and activates eNOS, then triggers an increase in NO production in minutes.

Insulin resistance means the inability of insulin to have a normal biological effect on certain blood sugar levels. Insulin resistance causes hyperinsulinemia. Hyperinsulinemia predisposes to hypertension by increasing sodium reabsorption from the kidneys and stimulation of the sympathetic nervous system. Hyperinsulinemia causes impaired lipid profile. Insulin resistance is associated with impaired endothelial function.

Pregnant women with complications of hypertension have insulin resistance and are associated with metabolic changes. Relative hyperinsulinism in normal pregnant women is a picture of the possibility of Preeclamsia or hypertension in pregnancy. In a study assessing insulin resistance showed differences between women with hypertension in pregnancy and those who were pregnant with normal blood pressure.

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Insulin resistance has an important role in the pathogenesis of Preeclamsia. Hyperinsulinemia may be a direct predisposition to hypertension by increasing sodium reabsorption from the kidneys and stimulation of the sympathetic nervous system. Insulin resistance is associated with impaired endothelial function.

How insulin resistance increases the risk of Preeclamsia is unclear. Some allegations to explain this relationship include: increased insulin resistance will increases sympathetic tone and increased vascular smooth muscle. The effect of insulin resistance on blood pressure is demonstrated by the discovery of drugs that reduce insulin resistance (thiadolidinediones) also reduce blood pressure (Magee, L. A et al. 2014)

Insulin resistance will cause hyperinsulinemia and hyperinsulinemia will cause changes in lipid characteristics. Changes in lipid characteristics increase the incidence of oxidative stress. Lipid oxidation may interfere with endothelial function directly and indirectly through the effects of prostaglandins, including increased thromboxane synthesis and inhibition of prostacyclin synthesis. Increased LDL and triglycerides have the potential to cause endothelial function disorders.

Noureldeen, AFH et al (2014) reported that IR research could be used to predict the occurrence of Preeclamsia before the onset of clinical symptoms with good sensitivity and specificity. Sex hormone binding globulin (SHBG) as a marker of insulin resistance. In women who became Preeclamsia decreased SHBG levels (302 ± 130 vs 396 ± 186 nmol / l; $p < 0.01$) compared to control. The increase in IR in early pregnancy is associated with the incidence of Preeclamsia. SHBG is a glycoprotein produced by the liver. Insulin suppresses SHBG production so insulin levels are inversely proportional to SHBG levels. Serum SHBG levels are associated with insulin resistance as described by glikemic hiperinsulin. In contrast to other insulin markers SHBG can be used without fasting so it is often used in clinical conditions that do not require fasting such as prenatal care.

Women who become Preeclamsia have higher insulin levels than those who are normal during pregnancy. Obtained the average HOMA-IR at LOP 4.78 ± 5.07 and in normal pregnancy 1.11 ± 1.29, $p = 0.011$. The proportion of Preeclamsia events in the IR group (53.3%) and in the non-IR group (46.7%), $p = 0.005$ and OR = 16 confident intervals (1.65 - 154.59), showed a significantly different Preeclamsia incidence between IR with no IR, and IR risk factors 16 times caused the occurrence of Preeclamsia.(Stupin, JH dan B Arbian. 2014)

The results of this study are also in accordance with the results of studies obtained by several other researchers where insulin resistance is higher in Preeclamsia patients compared to normal pregnancy.

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Hyperinsuinemia associated with insulin resistance has a role in the pathogenesis of Preeclamsia, with an OR 16 CI 95% (1.65 - 154.59) means that women with IR have a risk of developing Preeclamsia 16 times more than women without IR.

V. CONCLUSION

The average HOMA-IR level in obese pregnant women is higher than in those who have normal body weight in the Late Onset Preeclampsia

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