Hepcidin and C-Reactive Protein Levels in Obese Patients with Severe Preeclampsia

Efendi Lukas[1*], Deviana Soraya Riu[1], Isharyah Sunarno[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia

KEYWORDS
Preelampsia, Hepcidin, C-Reactive Protein, Obese.

ABSTRACT:

Introduction: Obesity during pregnancy not only increases the risk of preeclampsia but also affects the iron status and inflamation of both the mother and the fetus. Chronic inflammation associated with obesity can increase the production of hepcidin, which in turn reduces iron absorption. However, the relationship between hepcidin and CRP in obese preeclampsia pregnant women remain understudied.

Objectives: This study aimed to assess the relationship between hepcidin levels and C-reactive protein in obese and non-obese preeclamptic pregnant women.

Methods: The research was conducted cross-sectionally, with a total of 80 samples collected from 45 obese preeclamptic mothers and 35 non-obese preeclamptic mothers. Hepcidin and CRP levels were examined using the ELISA method, examination was conducted using Quantikine reagents for hepcidin and Roche reagents for CRP.

Results: The results we obtained show that the average hepcidin levels in the obese preeclamptic pregnant women group were higher than in the non-obese group, namely 28030.00 pg/ml vs 27315.00 pg/ml ($p > 0.05$), but this difference is not significant. These results indicate that in obese preeclamptic pregnant women, there is a stronger inflammation compared to the non-obese preeclamptic group. The average CRP levels we found in obese preeclamptic pregnant women were 31.89 mg/L, while in the non-obese preeclamptic group, it was 42.03 mg/L ($p > 0.05$). Although the CRP levels in the obese preeclamptic group were lower than in the non-obese preeclamptic group, this difference did not show a significant relationship

Conclusions: Obese preeclampsia patients exhibit elevated levels of hepcidin, which are positively correlated with the levels observed in non obese preeclampsia patients indicating that an inflammatory process occurs in both the obese and non-obese groups of preeclampsia patients.

1. Introduction

Preeclampsia, a leading cause of maternal and fetal morbidity and mortality worldwide, has shown a concerning increase in incidence, particularly in populations affected by the obesity pandemic Studies show that pregnant women with a high body mass index (BMI) have a greater risk of developing preeclampsia compared to those with a normal BMI.(Olson et al., 2019; Spradley et al., 2015)
Among the various theories explaining the pathogenesis of preeclampsia, the role of systemic inflammation is particularly significant. Pro-inflammatory cytokines and biomarkers, such as hepcidin and CRP, are emerging as key players in the disease's progression. but there are many theories related to the pathogenesis of preeclampsia, including vasoconstriction, endothelial cell injury, and systemic inflammatory response. Along with the theory of the inflammatory system in preeclampsia, the concentration of pro-inflammatory cytokines will increase in the plasma as a sign of preeclampsia. Several pre-existing maternal conditions are risk factors for the occurrence of preeclampsia, including

obesity. A recent meta-analysis study reported that the odds ratio (OR) for overweight women experiencing preeclampsia is 1.71 (95% CI 1.52 – 1.91) and 2.48 for obese women (95% CI 2.05 – 2.90).(He et al., 2020)

Hepcidin is a peptide hormone produced by the liver and plays a crucial role in regulating iron homeostasis. Hepcidin production is influenced by the body's iron status, erythropoiesis, and inflammation. In inflammatory conditions, such as in preeclampsia, hepcidin levels tend to increase. Elevated hepcidin can disrupt iron absorption and its release from macrophages, potentially leading to iron deficiency. Research shows that pregnant women with preeclampsia have higher hepcidin levels compared to pregnant women without preeclampsia. (Pagani et al., 2019; Ssewanyana et al., 2023)

Obesity during pregnancy not only increases the risk of preeclampsia but also affects the iron status of both the mother and the fetus. Chronic inflammation associated with obesity can increase the production of hepcidin, which in turn reduces iron absorption. Research shows that obese pregnant women have higher hepcidin levels and lower iron status compared to non-obese pregnant women. (Bandyopadhyay et al., 2022; Shaji Geetha et al., 2022a)

C-reactive protein (CRP) is an inflammatory marker commonly used to assess the level of inflammation in the body. High levels of CRP during pregnancy have been associated with an increased risk of preeclampsia. Obesity is also known to increase CRP levels, reflecting the presence of chronic systemic inflammation. Studies show that obese pregnant women have higher CRP levels compared to non-obese pregnant women. The relationship between hepcidin and CRP in obese preeclampsia pregnant women is an important focus of this research(Hamadeh et al., 2021; Mohaupt, 2015; Rebelo et al., 2013)

2. Methods

The research was conducted cross sectionally from November 2023, to June 2024. Sample collection was carried out at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital in Makassar, after obtaining approval from the ethics and research committee of the Faculty of Medicine, Hasanuddin University, no. 806/UN 4.6.4.5.31/PP36/2023. The study population was divided into two groups: obese women with severe preeclampsia (n=45) and non-obese women with severe preeclampsia (n=35).

Blood sampling was conducted after obtaining consent from the research subjects and meeting the inclusion criteria, namely a single live pregnancy and a gestational age of over 20 weeks. The criteria for severe preeclampsia are according to the American College of Obstetricians and Gynecologists (ACOG) guidelines from 2017, and the criteria for obesity are according to the World Health Organization (WHO) guidelines, which is when the body mass index is > 30 kg/m². A 5 cc venous blood sample was taken, and the hepcidin level test was conducted at the Prodia Laboratory using the enzyme-linked immunosorbent assay (ELISA) method with Quantikine reagents, and the level was expressed in pg/ml. The CRP level test used hs CRP cobas Roche reagents, and the level was expressed in mg/L.

The collected data were analyzed using SPSS version 23 (IBM Corporation, Armonk, NY, USA), The Mann-Whitney U test was applied to compare hepcidin and CRP levels between obese and non-obese groups. Correlation analysis was performed using Spearman's correlation coefficient based on data normality, with all statistical tests considered significant if the p-value < 0.05.

3. Results

There was no significant difference in risk factors for preeclampsia between the two groups (Table 1). Although obesity is a risk factor for preeclampsia, blood pressure at the time of diagnosis may not differ significantly between obese and non-obese pregnant women (Table 2). Hepcidin level in the obese preeclampsia group is slightly higher than the non-obese group. The difference in CRP levels between the obese and non-obese preeclampsia groups in this study also shows an interesting

pattern, with the median CRP level in the non-obese group being higher compared to the obese group (Table 3), Hepcidin and CRP have a positive correlation in this study (Table 4)

Table. 1 Risk factors of preeclampsia

Risk Factors	Category	Obese preeclampsia (BMI≥30) n = 45	Non obese preeclampsia n= 35	p-value
Nullipara	Yes	19 (23.8)	18 (22.5)	0,26
	No	16 (20.0)	27 (33.8)	
Age > 35 years	Yes	9 (11.3)	13 (16.3)	0,805
	No	26 (32.5)	32 (40.0)	
Preeclampsia history in family	Yes	0	0	N/A
	No	34 (43.8)	45 (56.3)	
Preeclampsia in previous pregnancy	Yes	2 (2.5)	5 (6.3)	0,654
	No	33 (41.3)	40 (50)	
Twin pregnancy	Yes	0	0	N/A
	No	34 (43.8)	45 (56.3)	
Diabetes melitus	Yes	1 (1.3)	0	N/A
	No	34 (42.5)	45 (56.3)	
Chronic hypertension	Yes	3 (3.8)	6 (7.5)	0,724
	No	32 (40.0)	39 (48.8)	
Kidney diseases	Yes	0	0	N/A
	No	34 (43.8)	45 (56.3)	
SLE	Yes	0	0	N/A
	No	34 (43.8)	45 (56.3)	
Anti phospholipid Syndrome	Yes	0	0	N/A
	No	34 (43.8)	45 (56.3)	

Table 2. Physical examination and weight gain

Physical Examination	Obese preeclampsia (BMI>30) n = 45	Non obese preeclampsia n= 35	P value
Weight gain (kg)	10 ± 8	9 ± 4	0.322
Weight before pregnancy (kg)	82 ± 18	63 ± 16	<0,001
Body mass index (kg /m2)	35.71 ± 5.06	25.23 ± 3.71	<0,001
Systolic blood pressure (mmHg)	170 ± 20	170 ± 21	0.468
Diastolic blood pressure (mmHg)	100 ± 18	110 ± 20	0.150
Mean arterial pressure (mmHg)	123.3 ± 22	126.7± 23	0.455

Table 3. Hepcidin levels and C-Reactive Protein (CRP) in obese preeclampsia and non-obese preeclampsia groups.

Parameter	Obese preeclampsia			Non Obese preeclampsia			**P value**
	Median	Min	Max	Median	Min	Max	
Hepcidin (pg/ml)	28.030	992	104.141	27.315	860	109.688	0,254
CRP (mg/ml)	7,40	0,70	135,40	17,20	0,20	197,20	0,449

* Mann Whitney test

Table 4. Correlation of hepcidin levels and CRP in the obese preeclampsia group and non-obese preeclampsia group

Correlation	Obese preeclampsia		Non Obese preeclampsia	
	r	P value	r	P value
Hepcidin- CRP	0,437	0,009	0,360	0,015

* Spearman correlation test

4. Discussion

Obesity in pregnant women is associated with inflammatory dysregulation and metabolic disorders that can worsen the condition of preeclampsia. Moreover, obesity can also cause fat accumulation in the placenta. In this context, inflammation plays a crucial role in the pathophysiology of preeclampsia, where inflammatory biomarkers such as C-Reactive Protein (CRP) and hepcidin have the potential to serve as clinical indicators for monitoring this condition in both obese and non-obese pregnant women with preeclampsia. This study aims to

identify the roles of these two biomarkers in predicting and understanding the mechanisms of severe preeclampsia in obese and non-obese pregnant women. (Olson et al., 2019)

Hepcidin is crucial to the pathophysiology of preeclampsia, particularly through controlling iron metabolism. The liver produces hepcidin, a crucial hormone in iron metabolism, and inflammation can affect its levels. Iron dysregulation and oxidative stress are two factors that exacerbate preeclampsia, and hepcidin levels frequently rise in pregnant women with preeclampsia.(Pagani et al., 2019)

It has also been demonstrated that pregnant women with preeclampsia, particularly those who are obese, have higher levels of hepcidin. High levels of hepcidin, the primary hormone controlling iron metabolism, in obese pregnant women with preeclampsia suggest a connection between inflammation and iron metabolism issues. Through inflammatory processes that prevent iron absorption, obesity exacerbates hepcidin regulation, resulting in a drop in blood iron levels. In obese pregnant women with preeclampsia, this may raise the risk of anemia and more serious consequences. The management of preeclampsia is made more difficult by the rise in hepcidin in obese pregnant women.(Chibanda et al., 2023; Fisher & Nemeth, 2017; Shaji Geetha et al., 2022b)

Low hepcidin levels during pregnancy are expected to optimize iron bioavailability for both the mother and the fetus, but inflammatory conditions during pregnancy such as preeclampsia are associated with increased hepcidin levels. The increase in hepcidin levels in preeclampsia patients may serve as a protective mechanism against the effects of excessive iron cytotoxicity, oxidative stress, and endothelial dysfunction. The rise in hepcidin levels is associated with increased oxidative stress occurring in preeclampsia conditions, especially in obese mothers who have a higher tendency for inflammation. This oxidative stress plays a role in worsening the severity of preeclampsia and potentially increasing the risk of cardiovascular complications in obese pregnant women. High levels of hepcidin also indicate significant iron metabolism dysfunction, but other studies found no significant difference in hepcidin levels between the preeclampsia group and normal pregnant women.(Ahmed et al., 2023; Amstad Bencaiova et al., 2019)

The increasing of hepcidin levels in pregnant women with preeclampsia, especially in the obese group, indicates a dysregulation of iron metabolism due to higher inflammation in obesity conditions. The role of hepcidin as a hormone regulating iron metabolism is crucial in understanding the development of preeclampsia in the obese group. High hepcidin levels in the obese preeclampsia group indicate that obesity exacerbates the dysregulation of iron metabolism commonly found in preeclampsia cases. (Abraham & Romani, 2022)

It is suspected that hepcidin will only increase very high in pregnant women with a very high BMI. We found the average body mass index (BMI) in the obese preeclamptic pregnant women group to be 35.71 + 5.06 kg/m², which may be the reason why in this study we found no significant difference in hepcidin levels between the obese preeclamptic group and the non-obese preeclamptic group. A study conducted in China found no difference in hepcidin levels between obese women before pregnancy and women with normal weight during pregnancy.(Jones et al., 2021; Koenig et al., 2020)

From the perspective of variations in hepcidin and CRP levels, this study shows that the range of CRP levels in the non-obese group is wider, from 0.20 to 197.20 mg/ml, compared to the obese group, which ranges from 0.70 to 135.40 mg/ml. This variability is in line with the study conducted by Cepeda-Lopez et al. (2021), which showed that individual physiological and metabolic differences in the non-obese preeclampsia group contribute to greater inflammatory variation. The high levels of CRP in these non-obese individuals may be due to a stronger inflammatory mechanism of preeclampsia, independent of obesity status. (Cepeda-Lopez et al., 2011)

This finding contrasts with some previous research, such as the study conducted by Jones et al. (2021), which indicated that obesity tends to elevate CRP levels, suggesting the presence of chronic inflammation. This discrepancy may be attributed to differing inflammatory responses depending on the severity of preeclampsia, which could be more dominant than the influence of obesity in increasing CRP levels.(Jones et al., 2021)

Recent studies have shown an increase in CRP levels in pregnant women with preeclampsia, both obese and non-obese, compared to normotensive pregnant women. CRP is an inflammatory protein produced by the liver in response to inflammation, and its levels are known to be higher in chronic inflammatory conditions such as obesity. In pregnant women with severe preeclampsia, CRP levels often show a more significant increase due to the more severe systemic inflammation that occurs. In cases of preeclampsia, the increase in CRP is related to the severity of the disease and its accompanying complications. Obesity exacerbates the existing chronic inflammation, resulting in higher CRP levels compared to mothers with normal body weight.(Guan et al., 2023)

Regarding CRP levels, the data show that the median CRP level in the non-obese preeclampsia group (17.20 mg/ml) is higher compared to the obese group (7.40 mg/ml), although this difference is also not significant (p=0.449). CRP is an inflammatory marker that often increases in chronic inflammatory conditions such as obesity and preeclampsia. However, these results may indicate that in the non-obese group, preeclampsia causes a greater increase in CRP as a response to more severe systemic inflammation. Genchevha et al. found increased CRP levels in patients with gestational hypertension compared to the control group, but not in the preeclampsia group.(Gencheva et al., 2021)

The insignificance of the differences in hepcidin and CRP levels between the obese and non-obese preeclampsia groups may indicate that these two biomarkers are influenced by other complex factors beyond obesity. Factors such as the severity of preeclampsia, metabolic status, and genetics of the pregnant woman could be variables that influence the levels of these biomarkers.

Various studies have identified the role of obesity in increasing the severity of preeclampsia, including through elevated levels of inflammatory biomarkers such as CRP and hepcidin. In pregnant women who are obese, a higher inflammatory response can exacerbate endothelial dysfunction and lead to more severe hypertension. This mechanism can explain why obese pregnant women are more susceptible to severe preeclampsia compared to non-obese women. Therefore, monitoring CRP and hepcidin levels in pregnant women with preeclampsia can be an important step in identifying and preventing further complications.(Gencheva et al., 2021; Jiménez-Osorio et al., 2023)

Overall, this study indicates that although obesity is often associated with increased levels of hepcidin, preeclampsia may be a stronger factor influencing these inflammatory biomarkers. Thus, these results reinforce the understanding that the pathophysiological mechanisms of preeclampsia can operate independently of the influence of obesity, as suggested by Stoffel et al. (2021) In their study on inflammation in preeclampsia, further research is needed to understand the complex interactions between obesity and preeclampsia in influencing inflammatory biomarkers during pregnancy, especially in the context of physiological and genetic differences in populations. (Stoffel et al., 2021)

We found a correlation between hepcidin levels and CRP in the obese and non-obese severe preeclampsia groups (Table 4). These findings are consistent with recent research showing a close relationship between hepcidin levels and CRP in inflammatory conditions in obese pregnant women. In the non-obese preeclampsia group, the correlation between hepcidin and CRP was also positive with a value of $r = 0.360$ and $p = 0.015$. This correlation indicates that, although lower than in the obese group, the relationship between hepcidin and CRP is also significant in the non-obese group. Other studies have also revealed that hepcidin and CRP tend to be associated in inflammatory conditions, including preeclampsia, regardless of obesity status.(Abraham & Romani, 2022; Ssewanyana et al., 2023)

These results indicate that hepcidin and CRP levels are correlated in mothers with preeclampsia, with a stronger relationship in those who are obese. This positive correlation indicates that hepcidin may be an important biomarker in assessing the level of inflammation in preeclampsia, especially in mothers with obesity. These findings could serve as a basis for more precise interventions in managing the risk of inflammation in obese preeclampsia.

Our study is limited by the lack of data on iron status and anemia, which are critical for understanding the interplay between hepcidin and iron metabolism in preeclampsia. Future research should incorporate these parameters, along with longitudinal designs, to explore causal relationships.

5. Conclution

Obese preeclampsia patients exhibit elevated levels of hepcidin, which are positively correlated with the levels observed in non obese preeclampsia patients indicating that an inflammatory process occurs in both the obese and non-obese groups of preeclampsia patients. The difference in correlation values between the two groups may reflect a higher level of inflammation in the obese preeclampsia group compared to the non-obese group.

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