

The role of C-Reactive Protein in the level severity of hyperemesis gravidarum

El papel de la Proteína C Reactiva en el nivel de gravedad de la hiperemesis gravídica

Ni Made Rosiyana^{1a*}, M. Aryadi Arsyad^{2b}, Saidah Syamsuddin^{3c}, Ni Luh Emilia^{4d}, Estelle Lilian Mua^{5d}, Robi Adikari Sekeon^{6d}, Meilin Angreyni^{7d}, Suratno Kaluku^{8e}, Bayu Azhar^{9f}, Sena Wahyu Purwanza^{10g}

SUMMARY

Introduction: Causes of Hyperemesis Gravidarum (HG) are unknown. C-Reactive Protein (CRP) is thought to play an important role in the occurrence of HG. This study is to determine the values of CRP in normal pregnant women and hyperemesis gravidarum (HG), CRP levels on HG severity, and to know the role of CRP in the severity of HG.

Methods: The study design was cross-sectional, with 50 first-trimester pregnant women taken as samples consisting of 25 normal pregnant women and 25 mothers with HG. Blood serum samples were collected using High Sensitivity CRP (hs-CRP) for CRP content. HG severity data were used by filling out the Unique Quantification Questionnaire Emesis/

Nausea (PUQE), divided into three groups: mild HG, moderate HG, and severe HG. Data analysis was conducted using the Mann-Whitney test, Kruskal Wallis, and Post Hoc Test.

Results: The results showed no difference between C-Reactive Protein levels between normal pregnant women and HG. However, there were different levels of CRP values mild, moderate, and severe HG. Although there was a doubling in CRP levels between mild HG and heavy HG, CRP levels were also found to be different in moderate HG and heavy HG, with a mean difference of 7,94 mg/L.

Conclusion: An increase in average CRP levels was found beyond the normal limit for those with heavy HG. Elevated levels of CRP played an important role in the context of specific HGs, particularly in severe HG. Therefore, examining inflammatory markers,

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ORCID ID: 0000-0002-1190-713X¹
ORCID ID: 0000-0002-3492-0599²
ORCID ID: 0000-0002-4331-1680³
ORCID ID: 0000-0003-1441-1575⁴
ORCID ID: 0000-0002-2868-9183⁵
ORCID ID: 0000-0001-5162-5009⁶
ORCID ID: 0000-0002-5597-6866⁷
ORCID ID: 0000-0001-5567-8028⁸
ORCID ID: 0000-0002-3662-737X⁹
ORCID ID: 0000-0001-5451-6000¹⁰

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^aAkademi Kebidanan Palu Sulawesi Tengah, Palu, Indonesia
^bSection of Physiology, Faculty of Medicine, Universitas Hasanuddin Makassar, Makassar, Indonesia
^cDepartment of Mental Medicine, Faculty of Medicine, Universitas Hasanuddin Makassar, Makassar, Indonesia
^dSekolah Tinggi Ilmu Kesehatan Bala Keselamatan Palu, Palu, Indonesia
^ePoltekkes Kemenkes Maluku, Ambon, Indonesia
^fSekolah Tinggi Ilmu Kesehatan Payung Negeri Pekanbaru, Pekanbaru, Indonesia
^gInstitut Teknologi Kesehatan Malang Widya Cipta Husada, Malang, Indonesia

*Corresponding Author: Ni Made Rosiyana
E-mail: maderosiyana@gmail.com

especially CRP levels, is expected to be considered supporting data in the pathogenesis of HG.

Keywords: *CRP, hyperemesis gravidarum, inflamasi.*

RESUMEN

Introducción: *Las causas de la hiperémesis gravídica (HG) son desconocidas. Se cree que la proteína C reactiva (PCR) desempeña un papel importante en la aparición de HG. Este estudio tiene como objetivo determinar los valores de PCR en mujeres embarazadas normales e hiperémesis gravídica (HG), los niveles de PCR en la gravedad de la HG y conocer el papel de la PCR en la gravedad de la HG.*

Métodos: *El diseño del estudio fue transversal, se tomaron 50 gestantes de primer trimestre como muestra conformada por 25 gestantes normales y 25 madres con HG. Las muestras de suero sanguíneo se recolectaron, y utilizando un PCR de alta sensibilidad (hs-PCR) se determinó el contenido de PCR. Los datos de gravedad de la HG se utilizaron mediante el llenado del Cuestionario Único de Cuantificación Emesis/Náuseas (PUQE), divididos en tres grupos: HG leve, HG moderada y HG grave. El análisis de datos se realizó mediante la prueba de Mann-Whitney, Kruskal Wallis y Post Hoc Test.*

Resultados: *Los resultados no mostraron diferencias entre los niveles de proteína C reactiva entre mujeres embarazadas normales y HG. Sin embargo, hubo diferentes niveles de valores de PCR en HG leve, moderada y severa. Aunque hubo una duplicación en los niveles de PCR entre la HG leve y la HG intensa, también se encontró que los niveles de PCR eran diferentes en la HG moderada y la HG intensa, con una diferencia media de 7,94 mg/L.*

Conclusión: *Se encontró un aumento en los niveles promedio de PCR más allá del límite normal para aquellos con HG abundante. Los niveles elevados de PCR desempeñaron un papel importante en el contexto de HG específicos, particularmente en HG grave. Por lo tanto, se espera que el examen de los marcadores inflamatorios, especialmente los niveles de PCR, se considere como datos de respaldo en la patogenia de la HG.*

Palabras clave: *PCR, hiperémesis gravídica, inflamación.*

INTRODUCTION

Nausea and vomiting in pregnancy can occur in 2/3 of pregnant women worldwide. The severe

form of nausea and vomiting in pregnancy is hyperemesis gravidarum (HG). Hyperemesis gravidarum can occur in 0.3 %-3.6 % of pregnant women (1). HG, which is severe nausea and vomiting, can cause dehydration, acid-base, electrolyte disorders, ketosis (2,3), and cancer with long-term effects associated with increased Human Chorionic Gonadotropin (HCG) hormone (4-6). In addition, HG can also cause low birth weight (7), small pregnancies and preterm births (8-10), and nerve development delays in children born (11-13).

The cause of HG is not known for sure, but the system of immune dysregulation is thought to be one of the factors that play a role in the occurrence of HG (11). Where are inflammatory markers cytokines such as TNF- α , interleukin-6 (IL-6) (14), C-reactive protein (CRP) (15), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) (16,17) and white blood cells it is known that it tends to increase in mothers with HG (15).

C-Reactive Protein (CRP), a marker of acute phase inflammation, has been found to increase the incidence of HG (15,18,19). But not all studies agree on the role of CRP in the incidence of HG, where the results of the study by Tunc et al. (20) and Akdag et al. (21) found no significant association between CRP levels and HG incidence.

There is still controversy over the use of CRP levels in maternal blood that can indicate the role of inflammation as one of the triggers of HG. In addition, the role of CRP levels in pregnant women with HG and the severity of HG is not yet known. For this reason, the researchers were interested to assess the role of CRP in the severity of HG.

METHODS

Design Study

This research was conducted in the obstetric care room and midwifery polyclinic at three hospitals and two health centers. This study is a form of observational study using a cross-sectional study design.

Population and Sample

The population in this study were 25 pregnant women who were treated or treated by road due to experiencing HG based on medical record diagnoses and 25 normal pregnant women based on medical record diagnoses that examined their health in the polyclinic. Selected by stratified sampling, which met the criteria for inclusion criteria, namely first-trimester pregnant women willing to become respondents by signing an informed consent issued by the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin with number UH1702121105, and exclusion criteria, namely twin pregnancies, maternal pregnancy, suffering from urinary tract infections, suffering from gastrointestinal and thyroid disease, and suffering from diabetes mellitus.

Method of Collecting Data

Data collection in this study was conducted in two ways: examining CRP levels and measuring the severity of HG experienced by respondents. Examining CRP levels was carried out by taking blood samples through the median acuity vein as much as 5 mL, then centrifuging for 10 minutes at a speed of 3 000 rpm to separate the serum. The separated serum was taken as much as 0.1 mL for examination using ELISA High Sensitivity C-Reactive Protein (hs-CRP) (Diagnostics Biochem Canada Inc. CAN-CRP-4360, Version 5.0). In addition, data on the severity of hyperemesis gravidarum were measured by filling out the Pregnancy Unique Quantification of Emesis/Nausea (PUQE) questionnaire (22). The interpretation of the results of the score calculation is between 4-15 points for HG patients, which are then grouped into three groups, namely mild HG (≤ 6) (n=2), moderate HG (7-12) (n=12), severe HG (13-15) (n=11).

Data Analysis

Data were processed using SPSS for Windows version 16. To find out the difference in CRP levels in normal pregnant women and pregnant women, HG was used in the “Mann-Whitney” bivariate analysis. To find out the difference in

CRP levels in the HG group based on the severity of HG, the bivariate analysis “Kruskal Wallis” was used, which then carried out the Mann Whitney Post Hoc test to determine the difference in CRP levels between groups of the severity of HG.

RESULTS

Table 1 shows that the mean CRP level of blood in normal pregnant women (10.13 mg/L) does not differ greatly from the mean blood CRP in pregnant women with HG (10.34 mg/L), where the average difference between the two groups is 0.21 mg/L. To determine whether there is a difference in CRP levels between normal pregnant women and pregnant women with HG, then the analysis is carried out using the Mann-Whitney test with a level of confidence ($\alpha=0.05$), obtained p-value=0.438 then statistically known there was no significant difference between CRP levels in normal pregnant women and pregnant women with HG.

Table 1

Differences in C Levels of Reactive Protein in Normal Pregnant Women and Hyperemesis Pregnant Women

Lab Results	Group of Pregnant Women		p-value
	Normal	Hyperemesis Gravidarum	
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
CRP Level	10.13 \pm 9.71	10.34 \pm 6.34	0.438

Normality Test: data is abnormally distributed ($p < 0.005$)
 * Mann Whitney; n=50 people (normal n=25 and HG n=25); CRP examination of blood serum samples was carried out using ELISA High Sensitivity C-Reactive Protein (hs-CRP) (Diagnostics Biochem Canada Inc. CAN-CRP-4360, Version 5.0) with unit yields of mg/L. Grouping of pregnant women based on the respondent's diagnosis in the medical record.

Data analysis based on Table 2 shows that the mean CRP level in heavy HG (14.95) is greater than the mean Medium CRP (6.60) and mild (7.40). From the results of the Kruskal Wallis test, p-value=0.014, which means that there is a difference between mild, moderate, and severe CRP levels in HG.

Table 2

Comparison of CRP Levels in the Hyperemesis Gravidarum Group Based on the Level of Hyperemesis Gravidarum

Lab Result	Status Of Hyperemesis Gravidarum			p-value
	Mild $\bar{x} \pm SD$	Moderate $\bar{x} \pm SD$	Severe $\bar{x} \pm SD$	
CRP Level	7.40 ± 0.20	6.60 ± 3.64	14.95 ± 6.31	0.014

Normality Test: data is abnormally distributed ($p < 0.005$); * Kruskal Wallis Test; $n=25$ (HG ring $n=2$; HG is $n=12$; HG weight $n=11$); CRP examination of serum blood samples was initiated by using High Sensitivity C-Reactive Protein (HS-CRP) ELISA (Diagnostics Biochem Canada Inc. CAN-CRP-4360, Version 5.0) with a unit of the yield of mg/L. HG status was assessed based on the PUQE score questionnaire (mild ≤ 6 , moderate 7-12, severe 13-15)

The statistical test results in Table 3 show that the mean CRP levels in mild HG pregnant women did not differ significantly from the CRP levels of the group of moderate HG pregnant women, with a mean difference of 0.8 mg/L and p -value=0.144 which means there is no difference between CRP levels in mild and moderate HG pregnant women. The difference in CRP levels in the group of pregnant women with mild HG compared with the group of heavy HG pregnant women was also known not to have a significant difference (p -value=0.167), but when viewed from the average number of heavy CRPHG levels

(14.95 mg/ L), there were two greater than the CRP level in women with mild HG (7.40 mg/ L), with a difference of 7.55 mg/ L. While the difference in CRP levels in moderate and severe HG severity is known to mean CRP levels in moderate HG (6.60 mg/L), where 7.94 mg/L is smaller than the average CRP level in pregnant women with severe HG (14.95 mg/L), besides that from the analysis of the data it was found that there were significant differences between CRP levels in pregnant women with moderate and severe HG (p -value=0.007).

Table 3

Mean Differences in CRP Levels in the Hyperemesis Gravidarum Group Based on the Level of Hyperemesis Gravidarum

Lab Result	Status of Hyperemesis Gravidarum					
	Mild vs Moderate		Mild vs Severe		Moderate vs Severe	
	Mean Different	p-value	Mean Different	p-value	Mean Different	p-value
CRP Level	0.8	0.144	7.55	0.167	8.35	0.007

Mann Whitney Post Hoc Test; $n = 25$ (HG ring $n = 2$; HG is $n = 12$; HG weight $n = 11$); CRP examination of serum blood samples was initiated by using High Sensitivity C-Reactive Protein (HS-CRP) ELISA (Diagnostics Biochem Canada Inc. CAN-CRP-4360, Version 5.0) with a unit of the yield of mg/L. HG status was assessed based on the PUQE score questionnaire (mild ≤ 6 , moderate 7-12, severe 13-15).

DISCUSSION

CRP is a marker of acute phase inflammation synthesized by the liver (23), which is known to play a role in the occurrence of HG (15). The role of CRP levels in the occurrence of HG is also indicated by the results of the previous study (18), which found higher CRP levels in HG compared to normal pregnant women (1.95 vs 0.56). Furthermore, these findings are reinforced

by the study by Kurt et al. (19), who also found an increase in CRP levels (1.39-1.9 mg/L) in mothers with HG compared to the control group.

However, in this study, there was no significant difference in CRP levels in normal pregnant women and pregnant women with HG ($p > 0.438$), with mean differences not much different (10.13 vs 10.34 mg/ L). These findings align with the research conducted by Tunc et al (13), which found that CRP levels were not much different

between mothers who had HG and normal pregnant women with a mean ratio of 0.184-0.384 mg/L. In addition, research conducted by Akdag et al. (21) on 30 respondents with HG and 30 normal respondents who had the same characteristics also found that CRP levels in normal pregnant women were not much different from those of HG pregnant women (0.29 vs 0.47 mg/L) and found no difference between CRP levels in the study group and the control group.

In pregnancy, it is known that increased levels of the hormone estrogen cause excessive antibody production. The hormone estrogen is a hormone that increases in number during pregnancy triggered by the presence of the placenta (23,24). According to the researchers' assumption that there is no difference in CRP levels in normal pregnant women and HG mothers in this study, it is influenced by the hormone estrogen level, which also increases in pregnancy. Judging from the average CRP levels in normal pregnant women and HG mothers who are not much different, it can be assumed that the synthesis of CRP levels in normal pregnancies and HG is equally increased due to an increase in the hormone estrogen in pregnancy. Increasing the production of CRP levels in someone other than influenced by the hormone estrogen is also influenced by many other things such as the presence of chronic infections, the presence of metabolic syndrome suffered by respondents, pharmacological treatment, physical activity, and dietary patterns carried out by respondents (25,26).

In addition, there was no difference in CRP levels in the incidence of HG in this study, possibly due to a multifactorial influence on the occurrence of HG (27). One of the factors proposed as a cause of HG is endocrine factors. Endocrinology changes (specifically estrogen and progesterone, and HCG hormones) are known to play a role in the incidence of HG (27,28). The results of the research conducted by Biberoglu et al. (29) found that hormonal imbalances in pregnancy resulted in abnormalities, including the incidence of HG. In this study, no monitoring of estrogen, progesterone, and HCG levels was carried out, so there was no known difference in hormonal levels between normal pregnant women and women with HG in the study respondents.

The concentration of CRP levels in the blood in normal women is <10 mg/L (30). In this study,

there was a tendency to increase the average CRP level of blood in both normal pregnant women and pregnant women with HG. More than normal increases in CRP levels in normal pregnant women (10.13 mg/L) and pregnant women with HG (10.34 mg/L) indicate that both normal pregnant women and pregnant women with hyperemesis gravidarum experience the process of occurring inflammation.

The high CRP levels found by researchers both in normal pregnant women and pregnant women HG can be caused by the integration of the immune and endocrine systems. Increased levels of estrogen in pregnancy can stimulate excessive antibody production, causing the risk of autoimmune occurrence (23). An increase in the immune system in pregnancy is known to protect the fetus and decidua from impaired maternal immune systems (28).

Analysis of CRP levels in the severity of HG found a difference between the severity of mild, moderate, and severe HG. When viewed from the difference in CRP levels between the severity of mild and severe HG, it was seen that the average CRP level in mild HG was two times lower than the CRP level in severe HG. In addition, differences in CRP levels were also found in moderate and severe HG ($p = 0.007$) with a mean difference of 8.35 mg/L. This finding shows that the difference in CRP levels in each pregnant woman will affect the severity of hyperemesis gravidarum experienced by the pregnant woman.

Monitoring CRP levels can be used to assess an initial inflammation and can also be used to monitor the activity of an illness (31). Elevated levels of inflammatory markers such as CRP can stimulate histamine, serotonin, dopamine, and cholinergic receptors, which are Neuroanatomical (Area Postrema for CTZ). The response from CRP stimulation then provides feedback to the gastrointestinal tract through the vagus efferent to stimulate the gastrointestinal tract to produce histamine, serotonin, dopamine, and cholinergic, causing vomiting (32).

Although there was an increase in CRP levels, the increase did not increase in balance from mild HG to severe HG. This differs from the results of research conducted by Kurt et al. (19), who found an increase in CRP levels in proportion

to the severity of HG. This may be due to the imbalance in the number of respondents in each group of HG severity in this study and the difference in the use of CRP levels associated with the sensitivity of the device in detecting CRP levels in the blood.

This study also found CRP levels that exceeded normal values in the incidence of severe HG (14.03 mg/L > 10.00 mg/L), which means that an inflammatory process occurs in severe HG. An increase in CRP levels in the incidence of HG seems to play a role in the occurrence of severe hyperemesis gravidarum. It is associated with inflammation, one of the causes of vomiting, by causing stimulation to center vomiting (33). Immune system enhancement is also known to cause a decrease in gastric totality, leading to *Helicobacter pylori* development (34). The presence of *Helicobacter pylori* is known to worsen the incidence of HG (34) and is associated with the pathogenesis of HG events (35).

In addition, Schwedler et al. (36) found a close relationship between an increase in CRP levels and oxidative stress due to the increasing production of reactive oxygen species (ROS). Oxidative stress in the incidence of HG was found to increase oxidant levels (37). Another study found that oxidative stress stimulates the synthesis of various trophoblastic proteins, such as HCG and estrogen (38). This causes an increase in HCG and estrogen levels in the incidence of HG, which will further aggravate the incidence of HG experienced by a pregnant woman.

CONCLUSION

Based on the research results, it appears that the levels of C-reactive protein are not different between normal pregnant women and pregnant women with HG. But CRP levels differed in the severity of mild, moderate, and severe HG. Specific differences were found in moderate and severe HG, and CRP levels doubled between mild and severe HG. In addition, heavy HG found an increase in CRP levels that exceeded the normal limit. It seems that an increase in CRP levels plays an essential role in the occurrence of HG, especially in severe HG. Inflammatory markers, especially CRP levels, can be used as supporting data in the pathogenesis of HG.

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