

ORIGINAL ARTICLE :

Relationship between BMI and β -hCG levels with hyperemesis gravidarum in Manado, Indonesia**Inne Mamesah, Maria Loho, Eddy Suparman**Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sam Ratulangi, Manado, Indonesia
Indonesia**ABSTRACT****Objectives:** The main objective of this study was to determine the relationship between BMI and β -HCG levels with hyperemesis gravidarum.**Materials and Methods:** This study was a case control study which compares between BMI and β -Hcg levels of patients with hyperemesis gravidarum and without hyperemesis gravidarum. This study was conducted at Obstetric and Gynecology Department of Medical Faculty of Sam Ratulangi University in Manado. This study was conducted on September - November 2018 and participated by 33 pregnant women with hyperemesis gravidarum and 33 pregnant women without hyperemesis gravidarum which were included in accordance to the inclusion criteria and signed the informed consent to participate in this study.**Results:** The percentage of patients with Hyperemesis Gravidarum within the age group of 20 -35 years old were 23 patients (69.69%). The highest number of patients without Hyperemesis Gravidarum were within age group of 20 - 35 years old as many as 28 patients (84.84%). Hyperemesis Gravidarum was found the most in normal BMI group, which was 26 patients (78.78%). The patients without hyperemesis gravidarum were also found in the highest number in the normal BMI group, 21 patients (63.63%). T-test showed that there was no significant difference in BMI of group with positive HEG and negative HEG ($p = 0.027$). Spearman Correlation Test had been conducted to show relationship between β -hCG levels, and there was a strong correlation between gestational age and β -Hcg levels ($r = 0,764$; $p = 0,000$), which means β -hCG level increased along with gestational age.**Conclusion:** There was significant relationship between β -hCG and Hyperemesis Gravidarum. There was also a significant relationship between gestational age and β -hCG Levels which mean the increase of β -hCG level is along with the increase of gestational age. There was no significant relationship between BMI and Hyperemesis Gravidarum.**Keywords:** Hyperemesis Gravidarum, BMI, β -hCG**ABSTRAK****Tujuan:** Tujuan dari penelitian ini adalah untuk mengetahui apakah terdapat hubungan antara IMT dan kadar β -HCG dengan hiperemesis gravidarum.**Bahan dan Metode:** Penelitian ini merupakan penelitian kasus kontrol dengan membandingkan antara IMT dan kadar β hCG pada pasien hiperemesis gravidarum dan tanpa hiperemesis gravidarum. Penelitian dilakukan di departemen Obstetri dan Ginekologi Fakultas Kedokteran Universitas Sam Ratulangi Manado. Penelitian ini dilaksanakan pada bulan September – November 2018 diikuti oleh 33 orang wanita hamil dengan hiperemesis gravidarum dan 33 orang wanita hamil tanpa hiperemesis gravidarum yang semuanya memenuhi kriteria dan menandatangani formulir persetujuan untuk ikut dalam penelitian ini.**Hasil:** Dari data di atas diketahui bahwa presentasi pasien dengan hiperemesis gravidarum berada pada kelompok umur 20-35 tahun yaitu sebanyak 23 orang (69,69%). Untuk pasien tanpa hiperemesis gravidarum paling banyak berasal dari kelompok umur 20-35 tahun yaitu sebanyak 28 orang (84,84%). Presentase IMT pasien dengan hiperemesis gravidarum terbanyak pada kelompok IMT normal yaitu sebanyak 26 orang (78,78%). Untuk pasien tanpa hiperemesis gravidarum terbanyak pada kelompok IMT normal yaitu sebanyak 21 orang (63,63%). Uji t menunjukkan bahwa tidak terdapat perbedaan bermakna kadar IMT pada kelompok HEG positif dan HEG negatif ($p = 0,184$). Kesimpulan tidak terdapat hubungan bermakna antara kejadian HEG (positif atau negatif) dengan IMT. Uji Mann-Whitney menunjukkan bahwa terdapat perbedaan bermakna antara kadar β -HCG kelompok HEG positif dan kelompok HEG negatif ($p = 0,027$). Dilakukan uji korelasi Spearman untuk menunjukkan hubungan antara kadar β -Hcg didapatkan bahwa ada korelasi kuat antara umur kehamilan dengan kadar beta-HCG ($r = 0,764$; $p = 0,000$), yang berarti dengan peningkatan umur kehamilan maka kadar beta-HCG pun meningkat.**Simpulan:** Terdapat hubungan bermakna antara β -hCG dengan hiperemesis gravidarum. Ada hubungan bermakna antara umur kehamilan dengan kadar β -hCG yang berarti dengan peningkatan umur kehamilan maka kadar beta-HCG pun meningkat. Berdasarkan data hasil penelitian tidak terdapat hubungan bermakna antara IMT dengan hiperemesis gravidarum..**Kata kunci:** Hyperemesis Gravidarum, IMT, β -hCG***Correspondence:** Inne Mamesah, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sam Ratulangi, Manado, Indonesia Indonesia.

INTRODUCTION

Hyperemesis gravidarum is a state of nausea and vomiting that occurs in early pregnancy up to 20 weeks of gestation. When severe vomiting happens, dehydration, acid-base disorders, electrolytes imbalance and ketosis can occur. Nausea usually occurs in the morning, but in some cases, it may arise at any time of the day even at night. Excessive nausea and vomiting that occurs in pregnant women may result in electrolytes imbalance, weight loss (loss more than 5% of initial body weight), dehydration, ketosis, and nutritional deficiencies.^{1,2}

Causes of hyperemesis gravidarum are: hormone levels in pregnancy, such as β -hCG hormone, upper gastrointestinal tract dysfunction, psychological factors, liver abnormalities, autonomic nerve dysfunction, nutritional deficiencies, and *Helicobacter pylori* infection.³ Nutritional status is a balance between the intake of nutrients from food with the needs of body's metabolism. Each individual requires different nutrient intake. This requirement depends on the person's age, sex, activity in a day, body weight, and others. A person's nutritional status can be assessed using BMI (Body Mass Index). BMI describes the nutritional status of a person which can be categorized into underweight, normal and overweight.^{4,5,6}

The pathophysiology of hyperemesis gravidarum can be caused by the increase of human chorionic gonadotropin (hCG) hormone which may also be a contributing factor to nausea and vomiting.⁷ Increased levels of progesterone cause relaxation of the smooth muscle in gastrointestinal system which leads to a decrease in motility and emptying of the stomach. Hyperemesis gravidarum is a pregnancy complication that happens in the early age of gestation. If it occurs continuously, it may result in dehydration, electrolyte imbalance, and depletion of carbohydrate and fat reserves which being used for energy needs.^{8,9}

Excessive nausea and vomiting or hyperemesis gravidarum can be influenced by several factors including nutritional status, parity, psychological, and hormonal factors. For example, increased levels of hCG and leptin in first trimester pregnant women with a case of hyperemesis gravidarum happened because in early pregnancy there is an interaction between the autocrine and paracrine system. The release of hCG is also driven by estradiol, growth factors such as: FGF (fibroblast growth factor), EGF (epidermal growth factor), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), and interleukin-1, which are needed in the first trimester of pregnancy. All of these factors are able to trigger hyperemesis gravidarum in pregnant

women.¹⁰ According to the World Health Organization (WHO), in 2013, around 585.000 women died during pregnancy or childbirth. Ninety nine percent of maternal deaths due to childbirth or birth problems happens in developing countries. The maternal mortality ratio in developing countries is the highest with 450 maternal deaths per 100,000 live births compared to the maternal mortality ratio in 9 developed countries and 51 commonwealth countries. In 2016, 64 cases of hyperemesis gravidarum was recorded at Prof. R.D. Kandou Hospital, Manado, Indonesia among them 1 patient died due to Wernicke.^{11,12}

The main objective of this study was to determine the relationship between BMI and β -HCG levels with hyperemesis gravidarum.

MATERIALS AND METHODS

This was an analytical descriptive research with a case control approach conducted by collecting data on nutritional status and β hCG levels of hyperemesis gravidarum patients at Prof. Dr. R.D. Kandou Hospital, Manado, Indonesia. This study involved 66 research subjects who met the requirements and were willing to participate in the study. Sixty six research subjects consisted of 33 patients with hyperemesis gravidarum and 33 patients without hyperemesis gravidarum. The study sample was taken between September to November 2018.

The inclusion criteria included: normal pregnancy, being treated as hyperemesis gravidarum patient at Prof. Dr. R.D. Kandou Hospital, Manado, Indonesia willing to participate in this research and had signed research consent form. Subject should not have a history of psychiatric disorders nor suffering from any malignant diseases. Data collection was carried out by the researchers. Data analysis and processing was done by the researchers and statistical advisers. This was done both manually and using computer software the Statistical Program and Service Solution (SPSS) version 22.0.

RESULTS AND DISCUSSION

In early pregnancy, human chorionic gonadotropin (hCG) is produced mainly by the differentiated syncytiotrophoblast cells and is an important embryonic signal for maintaining pregnancy. During the first six weeks of pregnancy, hCG increases the secretion of progesterone, estradiol, and estron by transforming post ovulation ovarium to corpus luteum grvida.^{31,32,33} Subsequently, hCG also binds to its receptors and plays a special role in promoting angiogenesis in the uterine

endothelium, maintaining myometrial relaxation, and assisting the immunomodulation process through changes in dendritic cell activity, reducing T-cell activation and cytokine production, increasing recruitment of regulatory T cells (Treg), and increasing uterine natural killer (NK) cells proliferation at the frontier point of mother-fetus. The hCG metabolism is done by the placenta, liver, blood, and kidneys, which further determines the steady-state levels of the hormone itself. Measurement of serum or urine hCG levels can provide important information in various clinical circumstances, such as diagnosis and monitoring of pregnancy and its' related disorders, prenatal examinations, and gynecological cancers.^{33,34,35}

Table 1 shows that age-related characteristic of hyperemesis gravidarum patients was seen occurring at most within the age group of 20-35 years old which amounts

to 23 patients (69.69%), the confidence interval was - 2.861 – 3.164 and standard deviation was 1.508. As for patients without hyperemesis gravidarum, most came from the age group of 20-35 years old with 28 people in total (84.84%), the confidence interval was -2.863 – 3.166 and standard deviation was 1.508. The Shapiro-Wilk normality test showed that age was normally distributed throughout the group of patients with hyperemesis gravidarum and without hyperemesis gravidarum ($p = 0.872$ and 0.244), therefore t test was performed with the result that there was no significant difference between the group of patients with hyperemesis gravidarum and without hyperemesis gravidarum ($p = 0.920$). As a conclusion, there was no significant relationship between the incidence of hyperemesis gravidarum (positive or negative) with patient's age.

Table 1. Characteristics of pregnant women with and without hyperemesis gravidarum

Characteristics	Pregnant Women				
	Hyperemesis Gravidarum		Not Hyperemesis Gravidarum		
	Σ	%	%	Σ	
Age					
	<20 years old	2	6.06%	1	3.03%
	20-35 years old	23	69.69%	28	84.84%
	>35 years old	8	24.24%	4	12.12%
Education					
	Elementary School	2	6.06%	-	
	Middle School	4	12.12%	-	
	High School	24	72.72%	33	100%
	University	3	9.09%	-	
Occupation					
	Housewives	28	84.84%	29	87.87%
Working at non-governmental company		3	9.09%	1	3.03%
Civil servant		2	6.06%	3	9.09%
Parity					
	Primigravida	18	54.54%	25	75.75%
	Multigravida	15	45.45%	8	24.24%

Table 2. Body Mass Index (BMI) in pregnant women with and without hyperemesis gravidarum

Characteristics	Pregnant Women				
	Hyperemesis Gravidarum		Not Hyperemesis Gravidarum		
	Σ	%	%	Σ	
BMI					
	Underweight	1	3.03%	-	
	Normal	26	78.78%	21	63.63%
	Overweight	6	18.18%	12	36.36%

Table 3. Relationship between β -HCG levels and age of pregnancy

Age of Pregnancy (in weeks)	Average of β -HCG levels		
	Hyperemesis Gravidarum	Not Hyperemesis Gravidarum	
BMI			
	8 – 10	19.292	11.153
	11 – 13	225.087	45.938
	14 – 16	230.264	138.973

We found that 20-35 years old was the most frequent age group that suffers from this disease. This was because even though 20-35 years old is the right age group for pregnancy because they are already physically mature, psychological factors still play an important role as an influencing factor.^{36,37} The exact relation between psychological factors and hyperemesis gravidarum is not yet clear, however there is a possibility that a woman's refusal to become pregnant, fear of losing jobs, relationship breakdowns with spouse and so on, might be a contributing factor to the incidence of hyperemesis gravidarum. This is in line with the theory which stated that the incidence of hyperemesis gravidarum is more common in mothers aged 20-35 years old. This is suspected to be caused by the fact that this study did not take into account risk factors of hyperemesis gravidarum such as predisposing, organic and psychological factors into account. This is in agreement with the theory that the factors that influence the occurrence of hyperemesis gravidarum are predisposing factors (primigravida, overdistant uterine, hydramnion, multiple pregnancy, estrogen, high human chorionic gonadotropin hormone (HCG) and hydatidiform mole), organic factors (such as the invasion of chorionic villi in maternal circulation, metabolic changes due to pregnancy, decreased resistance on the mother's part and allergies) and psychological factors which include broken family and unwanted pregnancy.^{36,37,38}

Table 2 shows that patients with hyperemesis gravidarum were found mostly in the normal BMI group which amounts to 26 people (78.78%), followed by the overweight group with 6 people (18.18%), the confidence interval was 42791 – 2.1824 and the standard deviation was 65333. Whereas, patients without hyperemesis gravidarum were found at most in the normal BMI group with 21 people in total (63.63%), followed by the overweight group with 12 people (36.36%), the confidence interval was 42902 – 2.1835 and the standard deviation was 65333. Shapiro-Wilk normality test showed that the BMI data of the HEG positive and negative groups is normally distributed ($p = 0.066$ and 0.071), hence t test was performed. T-test showed that there was no significant difference in BMI levels between group of patients with hyperemesis gravidarum and without hyperemesis gravidarum ($p = 0.184$). Therefore, we can conclude that there was no significant relationship between hyperemesis gravidarum (positive or negative) with BMI. This results appeared to be a contradiction with the 2014 Hertje's study which stated that there was a relationship between nutritional status and the incidence of hyperemesis gravidarum in pregnant women.^{35,36,39} Similarly, it also contradicted the results of Ruri and Nurul's study in 2014 which stated that there was a

relationship between nutritional status and the incidence of hyperemesis gravidarum in pregnant women. Nutritional status is an important point that should be noted during pregnancy because nutritional factors greatly affect the health status of a mother which also affect fetal growth and development. Nutrition during pregnancy means foods or menu that fulfill all the nutrients need in a day and contain appropriate balanced nutrients that is just right and do not exceed the needed amount. Maternal health before and after pregnancy greatly determine the health of a pregnant women. Thus, in order for a pregnancy to go well, nutritional status of a mother at the time of conception must be in good condition, also she must obtain additional energy, protein, vitamins, and minerals during her pregnancy.^{37,40}

Table 3 shows that Shapiro-Wilk normality test showed that β -HCG in positive and negative HEG groups were not normally distributed (both $p = 0,000$), thus the non-parametric Mann-Whitney test was performed. The Mann-Whitney test showed that there was a significant difference in β -HCG levels between the positive and negative hyperemesis gravidarum groups ($p = 0.027$). As a conclusion, there was a significant relationship between incidence of hyperemesis gravidarum with β -HCG levels.

Spearman correlation test was performed and we found that there was a strong correlation between gestational age and β -hCG levels ($r = 0.764$; $p = 0,000$), the test result showed that an increase in gestational age would also be followed by the increase of β -hCG levels. This strong correlation was due to the finding that subjects who frequently had hyperemesis gravidarum also had high β -hCG levels and vice versa. One of the causes of hyperemesis gravidarum is an increase in β -hCG levels.^{41,42} Increased levels of this hormone are estimated to be steeply high, supported by the fact that women who are not pregnant only have an average of 5 IU β -hCG hormone, with sudden increase in a high amount, dizziness, nausea and vomiting are expected to happen. This is consistent with the level of β -hCG that continues to increase until the 14 – 16th week of pregnancy since the last day of menstruation. Most of pregnant women experience doubled level of β -hCG every 3 days. Increased levels of this hormone are usually characterized by nausea and dizziness that are often felt by pregnant women. β -hCG levels decrease and reach almost normal state a moment after delivery. However, usually this hormone stays above normal levels until 4 weeks after delivery or abortion.⁴³ Increased levels of β -hCG hormone in the first trimester of pregnancy is considered physiological conditions, because early pregnancy involves interactions between the autocrine and paracrine system. The release of β -

hCG is also driven by estradiol, growth factors such as: FGF (fibroblast growth factor), EGF (epidermal growth factor), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), and interleukin-1, which are needed in the first trimester of pregnancy. Therefore it can be concluded that the level of β -hCG hormone had a very strong influence on the incidence of hyperemesis gravidarum.^{41,42}

CONCLUSION

There was a significant relationship between β -hCG and Hyperemesis Gravidarum. There was also a significant relationship between gestational age and β -hCG levels, which means the increase of β -hCG level is along with the increase of gestational age. However, there was no significant relationship between BMI and Hyperemesis Gravidarum.

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