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Effect of High Levels of Human Chorionic Gonadotropin and Estradiol on Degree of Hyperemesis Gravidarum

Obstetrics and
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ABSTRACT

Background: Hyperemesis gravidarum is a condition that affects pregnant women (HG), serum levels of human chorionic gonadotropin (hCG) and estradiol are increased than in pregnant women who are not influenced.

Aim of the work: To learn more about how the elevation of human chorionic gonadotropin levels, and estradiol on the intensity of hyperemesis gravidarum during the first trimester.

Patients and methods: At El Hussein University Hospital, our prospective study was conducted from May 2020 to Nov. 2020; duration of the study was 7 months. The key sign of severe Hyper Emesis Gravidarum was a lengthy stay in the hospital (HG). The term "extended hospital stay" described as stay ≥ 4 days, as this cut-off value demarcates the top quartile of hospitalization time in our study population.

Results: There was a highly significant difference between cases with hospital stay < 4 days and cases with hospital stay ≥ 4 days in HCG cases. cases with longer stay have higher median HCG (300637) compared to cases with < 4 days stay (35029.5). However, no significant difference was found between cases with hospital stay < 4 days and cases with hospital stay ≥ 4 days was present as regard estradiol.

Conclusion: Hyperemesis gravidarum is a problem that involves severe nausea, vomiting, and anorexia during pregnancy that causes dehydration and weight loss in early pregnancy. Study found that there is a significant correlation between HCG and hyperemesis gravidarum and there is no significant correlation between estradiol and hyperemesis gravidarum and there is a strong link between presence of acetone and hyperemesis gravidarum intensity. So, The higher the levels of HCG the more the intensity of hyperemesis gravidarum ; (i.e high levels of HCG increase the severity of HG).

Keywords: Hyperemesis gravidarum, human chorionic gonadotrophine, Estradiol.

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INTRODUCTION

Emesis gravidarum, or pregnancy nausea and vomiting, is a multifactorial disorder that has major negative impact on the mother's and fetus's health and wellbeing. It is important to recognize, investigate, and treat this illness¹.

Symptoms of morning sickness, which are incorrectly called morning sickness, usually begin between the first and second missing menstrual period and last for about 14 to 16 weeks. Although nausea and vomiting are usually worse first thing in the morning, they can last all day².

In 0.3 % to 3% of pregnancies, hyperemesis gravidarum (HG) develops. HG is the second leading cause for women having live deliveries to be admitted to the hospital throughout their pregnancy.³

Female fetus sex, socioeconomic conditions, and ethnicity all play a role in hyper emesis gravidarum. HG is commonly distinguished from the more recurrent vomiting and nausea that develops during pregnancy, that impacts 80 % of all pregnant women . and necessitates hospitalization.⁴

HG's cause has yet to be determined. It appears to be multifactorial in nature, and it could be the result of a number of unconnected factors. Endocrine factors such as high human chorionic gonadotrophine, estradiol, and steroid hormone levels, gastrointestinal tract dysfunction, psychological causes, anatomical variations, genetic incompatibility, immunological factors, vitamin B6 deficiency, and trace-element deficiency are all thought to play a role in HG⁵.

Women who were unable to manage severe nausea and vomiting symptoms and chose abortion have been reported in case reports. Furthermore, over half of working pregnant women said that their job efficiency has been harmed by nausea and vomiting,

and around a quarter of these women have had to take time off work due to these problems⁶.

This is making it also socioeconomic problem. The reported estimated cost for hospital care alone is more 500 million \$ for the 59,000 women hospitalized with hyper emesis gravidarum in the United State annually⁷.

In women with HG, an elevated HCG level is linked to more severe vomiting and a delay in the clearance of aberrant biochemical markers. In HG, the level of maternal serum oestrogen is higher, but not in nausea and vomiting during pregnancy⁸.

PATIENTS AND METHODS

A prospective study was done at El Hussein University Hospital from May 2020 to Nov. 2020; duration of the study was 7 months. An extended hospitalization was used as a main evidence of intensity for Hyper Emesis Gravidarum (HG). An extended hospital stay was described as a stay ≥ 4 days, as this cut-off value demarcates the top quartile or length of hospitalization period in the study population.

This study includes 80 pregnant women during the first trimester of their ongoing pregnancy with HG. Hyper emesis gravidarum is usually described as persistent vomiting in pregnancy that interferes with fluid intake & nutrition. The maximum and minimum demarcations for HCG and estradiol were defined by using the power trend function in Microsoft office excel 2010 to graph a curve of right fit for the scatter grammes of HCG or estradiol levels vs. ultrasound-derived gestational age, as the power function produced the best fit curve depending on the r²-value. All points below the curve were designated "low," while those above it were marked "high." The providers were not informed about the HCG and estradiol levels.

On admission to the gynaecology ward, women with a suspected diagnosis of Hyper Emesis Gravidarum (HG) were enrolled. Following that, the patient's agreement was obtained after a brief explanation. HCG and estradiol levels were measured in venous blood as soon as feasible after admission, and the results were transferred to the hospital laboratory for analysis.

The Abbott AxSYM Total HCG test and the Abbott AxSYM Estradiol-6 assay were used to measure the levels of HCG and estradiol in the study participants. Using dilutional Techniques, the Abbott AxSYM Total HCG Assay assesses HCG levels up to 1000 mIU/mL (IU/L) and up to 1000000 mIU/ml using Dilutional Techniques, with a minimum detectable value of 2.0 mIU/mL (IU/L) as the least detectable concentration. A level of 10 pg/mL (36.7 pmol/L) is required for the Abbott AxSYM Estradiol-6 assay to be sensitive, and it can detect estradiol quantities up to 1000 pg/mL (3670 pmol/L). When the serum samples contained quantities that exceeded the upper limits of the above-mentioned ranges, the laboratory made the necessary dilutions.

Inclusion criteria: Pregnant in first trimester less than 14 Week as determined by ultrasound, medically free by history taking and by physical

examination, vomiting more than 3 times a day and causes dehydration and loss of weight more than 3 kg or 5% of body weight, singleton uncomplicated pregnancies and first hospitalization.

Exclusion criteria: Pregnant in 2nd and 3rd trimester, medical disorders especially that cause vomiting as cholecystitis, appendicitis and colitis, multiple pregnancies and non-viable pregnancy.

The following criteria were applied to all cases: Getting a complete history with stressing on age, parity and gestational age, clinical examination including body weight, abdominal examination to exclude other causes of vomiting, trans-abdominal or transvaginal pelvic sonogram to confirm gestational age, to exclude multiple pregnancies and gestational trophoblastic disease. Estradiol and HCG values were measured in the venous blood quickly following admission, and were given to our hospital's lab for analysis. Before beginning substantive treatment, a full blood count, ketones in urine (by dipstick), creatinine, urea, s.electrolytes, SGOT, SGPT and Bilirubin (total and direct) were all performed.

We decided to utilize ultrasound-derived gestational age and limit our trial to women who were 14 weeks pregnant, as HG usually manifests at this point and HCG levels peak late in the first trimester.

Questionnaire for patients included: name, age, parity, weight, gestational age, onset, duration of symptoms of H.G, hemoglobin (HB) level, acetone in urine.

In pluses, comments on urine analysis, liver enzymes, serum electrolytes, these data were obtained from patient sheets as all cases were admitted to the inpatient department.

Statistical method: The statistical analysis was carried out with the help of the SPSS v.15 program (SPSS Inc., Chicago, IL, USA). It was decided whether to compare means or ordinal variables using the Student t test, and the Mann-Whitney U test was employed for both. When dealing with categorical data, the Fisher exact test (2=2 datasets) and the x²-test (for datasets greater than 2=2 datasets) were utilized. For the purposes of adjusting for participant characteristics, laboratory data, and treatment mode, a multivariable logistic regression analysis (considering all factors with a crude p-0.2) was performed. A statistically significant result was defined as one with an adjusted p-value of less than 0.05. All tests use two-sided.

RESULTS

The table shows that the mean age, weight and GA among study cases was 26.9 ± 6.1 years, 67.2 ± 6.8 Kg and 10.8 ± 5.2 Weeks respectively. The median parity among cases was 2 children. Table1.

	Mean	±SD	Minimum	Maximum	Median	IQR*	
Age	26.9	6.1	16.0	45.0	26.0	22.0	30.0
Weight	67.2	6.8	55.0	85.0	67.5	62.0	71.0
Gestational age	10.8	5.2	7.0	14.0	10.0	8.0	12.0
Parity	2.2	1.7	.0	7.0	2.0	1.0	3.0

*interquartile range

Table 1: Description of personal and medical data among cases

The table shows that the mean HCG was 197434.8 ± 143817.9 with a median of 256127. HCG was high among 55% of cases. The mean estradiol was 2141 ± 946.5 with a median of 2200. Estradiol was high among 42.5% of cases. Table2.

		Mean	±SD	Minimum	Maximum	Median	IQR	
HCG		197434.8	143817.9	8153.0	403901.0	256127	31900	313191
Estradiol		2141	946.5	388.0	4913.0	2200.5	1291.0	2800.0
HCG	Normal	36	45%					
	High	44	55%					
Estradiol	Normal	46	57.5%					
	High	34	42.5%					

Table 2: Description of HCG and estradiol level among cases

More than half of cases (51.25%) were admitted in hospital for 4 or more days which mean sever hyper emesis gravidarum. Table 3

	N	%
Hospital stay	<4 days	39 48.75%
	≥4 days	41 51.25%

Table 3: Descriptions of duration of hospital stay among cases.

There was no significant correlation between personal and medical data on one hand (age, parity, GA, weight and Hb) and HCG level on the other hand. Table4

		HCG
Age	Rho*	-.051
	P	.684
	Sig	NS
Parity	Rho*	-.099
	P	.431
	Sig	NS
Gestational age	Rho*	.032
	P	.801
	Sig	NS
Weight	Rho*	-.015
	P	.904
	Sig	NS

HB	Rho*	-.065
	P	.604
	Sig	NS

Table 4: Correlation between personal data and HCG leve

There was no significant correlation between personal and medical data on one hand (age, parity, Weight and Hb) and estradiol level on the other hand, with exception of GA where it showed a positive significant correlation with estradiol level. Table 5

		Estradiol
Age	Rho*	-.216
	P	.082
	Sig	NS
Parity	Rho*	-.168
	P	.178
	Sig	NS
Gestational age	Rho*	.442
	P	.0001
	Sig	HS
Weight	Rho*	-.127
	P	.311
	Sig	NS
HB	Rho*	.185
	P	.137
	Sig	NS

*spearman correlation

Table 6: Correlation between HCG and estradiol level

There was no significant correlation between HCG and estradiol level this result against the scientific background. Table 6

		Estradiol
HCG	Rho*	.110
	P	.380
	Sig	NS

Table 6: Correlation between HCG and estradiol level

There was a highly significant difference between cases with hospital stay < 4 days and cases with hospital stay \geq 4 days as regard HCG, cases with longer stay have higher median HCG (300637) compared to cases with < 4 days stay (35029.5). However, no significant difference between cases with hospital stay < 4 days and cases with hospital stay \geq 4 days was present as regard estradiol. Table 7

	Hospital stay					Statistic	P	Sig	
	<4 days		\geq 4 days						
	Median	IQR*	Median	IQR*					
HCG	35029.6	23900.0	118461.0	300637.1	275665.5	361065.0	5.2**	.001	HS
Estradiol	1951.70	1059.60	2695.00	2552.60	1961.00	2925.00	1.87**	.061	NS

*Median (IQR)

**Mann Whitney test

Table 7: Comparison between cases with hospital stay < 4 days and cases with hospital stay \geq 4 days as regard HCG and estradiol.

DISCUSSION

The most frequent medical issue during pregnancy is nausea and vomiting, which is referred to as "morning sickness." Before the 20th week of pregnancy, approximately 75% of pregnant women experience vomiting⁹ and nausea.

Although the vast majority of pregnant women adjust to their position, vomiting and nausea can be severe in 10% of cases, leading to nutritional issues¹⁰.

To prevent maternal [vitamin B1 (thiamine) and K deficiency, Wernicke's encephalopathy] and fetal/neonatal [preterm birth, intrauterine growth restriction (IUGR), increased insulin resistance, psychological issues in adulthood] consequences, early detection of HG is critical¹¹.

Young age, psychiatric disease, female fetus, nulliparity, twin pregnancy, a previous pregnancy characterized by hyperemesis and hyperthyroidism have all been recognized as risk factors for hyperemesis gravidarum¹².

The cause of HG is uncertain, though it is assumed to be caused by hormonal, metabolic, mental, and psychosomatic diseases¹³.

Many ideas have been offered, implying its complex character for example, excessive levels of beta-chorionic gonadotropin (-hCG) and estradiol (E2), as well as psychological aspects¹⁴.

The study's main goal was to see how elevated concentrations of human chorionic gonadotropin and estradiol in the first trimester increased the intensity of hyper emesis gravidarum.

This prospective study was done in El Hussein Hospital and conducted at 80 pregnant women during the first trimester of their ongoing pregnancy with HG. They were subjected to detailed history, physical examination, ultrasonography, estimate serum HCG, and Serum estradiol, a full blood count, ketones in urine (by dipstick), creatinine, urea and electrolytes. An extended hospitalization was described as a stay ≥ 4 days, as this cut-off value demarcates the top quartile or period of hospitalization in the study population.

The present study showed that the mean age, weight and GA among study cases was 26.9 ± 6.1 years, 67.2 ± 6.8 Kg and 10.8 ± 5.2 Weeks respectively. The median parity among cases was 2 children.

While in Atmaca et al.¹⁰, the mean age, weight and GA among study cases was 26.54 ± 4.64 years, 56.79 ± 10.25 Kg and 9.18 ± 1.93 Weeks respectively.

The results demonstrated that the mean HCG was 197434.8 ± 143817.9 with a median of 256127. HCG was high among 55% of cases. The mean estradiol was 2141 ± 946.5 with a median of 2200. Estradiol was high among 42.5% of cases. More than half of cases (51.25%) were admitted in hospital for 4 or more days which mean severe hyper emesis gravidarum.

While in Oruç et al.¹⁵, the mean HCG was 95415.81 ± 44719.57 and the mean estradiol was 1677.84 ± 982.5 .

In this study, there was no considerable link between personal and medical data on one hand (age, parity, GA, weight and Hb) and HCG level and estradiol level on the other hand, with exception of GA where it showed a positive significant correlation with estradiol level.

Our results are supported by another study in which no significant linkage between physiological characteristics (age and weight) of respondents and HCG level¹⁶.

From the results of this study, there was no significant correlation between HCG and estradiol level this result against the scientific background for this finding this may be because number of patients was not enough.

The results demonstrated that no significant difference between cases with hospital stay < 4 days and cases with hospital stay ≥ 4 days as regard personal and medical data (age, GA, weight and Hb and parity).

Our findings support those of Atmaca et al.¹⁰, who found no clinically important variations in age, weight, height, gravidity, parity, or gestational age across the groups.

Unlu et al.¹⁷ discovered that the maternal age of HG patients was substantially greater than the control group.

There was a significantly considerable impact in this study between patients with hospital stay < 4 days and cases with hospital stay ≥ 4 days as regard HCG.

The relationship between hCG release and NVP signs is largely responsible for this result, both of which reach their apex during weeks 9 and 12 of pregnancy⁸.

In a review published in 2014, 18 studies found a relationship between elevated hCG levels and NVP or HG, 13 studies, on the other hand, revealed no such correlation.¹⁸

The Generation R study examined the amount of hCG in 8,195 participants and found a connection between hCG and common NVP signs¹⁹.

Our results supported by another study where serum level of HCG was significantly associated with severity of HG²⁰.

During a normal pregnancy, the placental tissues are densely invaded by mononuclear phagocytes and lymphocytes. trophoblast is the main origin of IL-6 during pregnancy which controls the secretion of hCG. Excessive activity of granulocytes and high concentration of trophoblast-derived cytokines might be involved in hyperemesis gravidarum. The impact of increased amounts of hCG in brain areas directly implicated in nausea or upper gastrointestinal tract or can rise thyroid hormone and estradiol which has the ability to affect nausea²¹.

Another study discovered a relationship between elevated hCG levels and the incidence of HG. The peak of hCG secretion in the first trimester coincides with the time of hyperemesis gravidarum that is generally seen. In women with twin and molar pregnancy which is associated with high HCG levels,

HG is more common than normal pregnant women²².

This result agrees with what of Derbent et al.²³ stated that “Hyperemesis gravidarum is associated with elevated levels of HCG, and such changes are independent of serum indicators of thyroid and liver function”. This opens field for further studies for predication of hyperemesis gravidarum and its outcome.

Also, this agrees with what Peled et al.²⁴ stated in a study investigated the effects of serious hyperemesis gravidarum on the triple test (alfa-feto-protein, estriol, Human Chorionic Gonadotropin(hCG)) screening results, the study resulted in “An increase in HCG levels in patients with severe hyperemesis gravidarum affects the triple test screen results. When counseling patients about their overall risk of chromosomal abnormalities, this information should be taken into account.”

On the contrary, Derbent et al.²³ concluded that no evidence of a link between high hCG levels and the development of HG. Also, there was no significant correlation between HG risk and HCG values¹⁷.

There was no proven link between hCG values and HG in a retrospective cohort study of 4,372 pregnant women after in vitro fertilization²⁵.

The current study results showed there were no significant difference between cases with hospital stay < 4 days and cases with hospital stay ≥ 4 days was present as regard estradiol.

This is in agreement with Tan et al.,²² who stated that high estradiol level was not associated with prolonged stay or with more severe HG. Women with hyperemesis have increased estrogen levels than women without hyperemesis, according to another study²⁶.

The fact that people with HG have high estrogen levels in their blood suggests that estrogen plays a role in the disease's development. Furthermore, the negative effects of estrogen-containing birth control pills include nausea and vomiting. Estrogen lowers intestinal motility and slows gastric emptying, as well as causing fluid shifts that lower stomach acidity and promote *H. pylori* growth. Pregnant smokers have decreased estrogen levels and are more likely to get HG²⁷.

The fact that women with HG are more likely to suffer nausea while taking contraceptives with a mix of estrogen and progesterone supports a function for the two hormones⁸. Total estradiol and HG studies, like hCG, are contradictory¹⁸.

Estradiol can lead to nausea in non-pregnant women by disrupting the frequency and direction of stomach contractions. The reason of this disturbance is uncertain, but it is thought to be hormone signaling, which disrupts slow-wave stomach rhythms significantly. The potency of cholecystokinin (CCK) is increased by raising the sensitivity of vagal CCK type A receptors in the gut, which raises the potency of cholecystokinin (CCK). CCK reduces food intake by slowing stomach emptying and activating afferent neurons of the subdiaphragmatic vagal nerve.

²⁸

CONCLUSION

Early-pregnancy hyperemesis gravidarum is a disorder highlighted by extreme vomiting, nausea, and anorexia, leading to dehydration and weight loss. There is a substantial association between HCG and hyperemesis gravidarum but, no significant association between estradiol and hyperemesis gravidarum, there is a substantial association between the presence of acetone and the severity of hyperemesis gravidarum, according to our findings. As a result, the higher the HCG levels, the more severe the hyperemesis gravidarum; (i.e. high levels of HCG increase the severity of HG).

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