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Assessment of the role of cholecystokinin in hyperemesis gravidarum and correlation with its severity

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Abstract

Background: Cholecystokinin is a gastrointestinal tract hormone synthesized and released from the upper part of small intestine and central nervous system.
Objective: To assess the cholecystokinin level in pregnancy with and without hyperemesis gravidarum and correlate it with the severity of condition.
Patients and methods: A case-control study conducted at AL-Yarmouk Hospital from March-November 2015. Sixty pregnant women were included, thirty with hyperemesis gravidarum and thirty pregnant women with normal pregnancy. For both groups, cholecystokinin level was measured with other hematological, biochemical, and hormonal parameters. The patient's group was classified according to the severity into mild, moderate, and severe according to classification posted by HER foundation.
Results: The mean level of cholecystokinin for the hyperemesis gravidarum group was significantly lower than control group ($p< 0.001$). Blood urea nitrogen and free thyroxin were significantly higher, while sodium, potassium, and thyroid stimulating hormone levels were significantly lower in comparison to control group. Twenty women with moderate hyperemesis gravidarum and ten with severe condition. The cholecystokinin was significantly lower in the severe cases vs. moderate cases (28.7 ± 11vs. 39.8 ± 13.9; $P=0.036$). The β-HCG is significantly higher in patients with severe cases than moderate cases.
Conclusion: serum cholecystokinin level was significantly reduced in hyperemesis gravidarum in comparison to the healthy pregnant women. This reduction is inversely correlated with the severity of the condition. This relationship with the severity triggers studies to evaluate the role of cholecystokinin as a marker of severity of hyperemesis gravidarum rather than a causal relationship.

Keywords: cholecystokinin, hyperemesis gravidarium, severity

INTRODUCTION

Hyperemesis gravidarum (HG) is a pregnancy problem that characterized by extreme persistent intractable nausea and vomiting with weight loss, sometimes reaches to a loss greater than 5 % body weight of that before pregnancy with nutritional deficiencies and dehydration that cause electrolyte disturbance and acid-base imbalance.[(1)]Unlike morning sickness, hyperemesis gravidarum may have an adverse effect on maternal and fetal health, it affects various areas of women health, including homeostasis, electrolytes, and kidney function.[(2)]The incidence of HG varies between 0.3-2.3 in pregnancy populations and it is the most common indication for admission to hospital in the first half of pregnancy and second to preterm labor for pregnancy in general.[(3),(4)]It usually began in the first trimester of pregnancy and some sufferers will experience severe symptoms until delivery and even their after.[(5)]The cause of HG remains controversial and there are many theories beyond it. It is thought that HG appears to occur as a complex interaction between biological, psychological, and sociocultural factors and severe form of HG may carry allot of maternal and fetal complication including weight loss, dehydration, metabolic ketoacidosis, anemia and peripheral neuropathies, Wernicke's encephalopathy, intrauterine growth retardation and fetal death.[(6),(7),(8)]

A cholecystokinin (CCK) is a hormone released from endocrine cells that line the mucosa of the upper small intestine in response to the amino acid and fatty acid in the chyme. It's a major hormone of the gastrointestinal tract that is responsible for gallbladder contraction and pancreatic enzyme secretion. It is found also in the central nervous system and peripheral nerves innervating the intestine and their CCK possibly acts as a neurotransmitter.[(9)]CCK constitute a feedback system were by it would regulate its' own release; i.e. whenever food would enter the duodenum the CCK would be released and this, in turn, would stimulate the gallbladder to contract and pancreatic enzyme to be secreted and at the same time it will inhibit gastric emptying. As a result, less food is delivered to the duodenum which in turn reduces the stimulus to further CCK release. In this supposition, CCK would play a role in gastrointestinal motility as the pregnant women with hyperemesis stop emesis usually when stop feeding orally and resume emesis when restart.[(10)]

PATIENTS AND METHODS:

This study is conducted in the Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital /Baghdad, from the 1st of March 2015 to the 1st of November 2015 after approval by the Obstetrics and Gynecological council of Iraqi Board for Medical Specialization and Department of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital. The study enrolled 60 pregnant women. An informed written consent from all the participants (patients and control), which included their permissions to use their clinical and laboratory data in this research, was taken before entering the study. For those below 18 years old, an informed written consent form was taken from both the participant and their husbands (in accordance with the local regulation of the Iraqi Council of Medical specialization and the IRB for the Al-Yarmouk Teaching Hospital Department of Gynecology for individuals below the legal age (i.e. 18 years)).

The study group consisted of patients who had been diagnosed with hyperemesis gravidarum , which characterized by severe, protracted nausea and vomiting associated with weight loss of more than 5% of prepregnancy weight, dehydration and electrolyte imbalances.[(11)]

Women with hyperemesis gravidarum severe to the degree that needs hospitalization were included, in any maternal and gestational age. Women with Multiple gestations, trophoblastic disease, or with any systemic disorders that may be responsible for her presentation, all were excluded.

Another group of healthy women who matched the above group in maternal and gestational age were included in the study as a control group from the antenatal care clinic, and we took an informed consent from them to be involved in this study.

Table (1): Severity Levels of Hyperemesis Gravidarum.*

Mild	Moderate	Severe
• Usually ends by mid-pregnancy • Weight loss is about 5% • Requires medications and sometimes IV fluids • Mother can continue some daily activities • Recovery may take a few months or more	• Often continues beyond mid-pregnancy but severity lessens • Weight loss is 5-10% (less with early treatment) • Requires medications, fluids, and sometimes nutrition by tube or IV • Mother is extremely fatigued and only able to do a few tasks • Recovery may take several months • Signs of trauma and changes in family planning often occur	• Often is constant and may be difficult to control with medications • Weight loss is 10-20% or more (less with early treatment) • Requires fluids, medications, and nutrition support for most of the pregnancy • Mother is exhausted, malnourished and unable to care for herself • Recovery can take several months to a year or more • Signs of trauma and changes in family planning are common • Delivery may be complicated and very difficult due to debility • Without treatment, baby may die and mother may proceed to organ failure

*adopted from the website of HER FOUNDATION
http://www.helpher.org/blog/severity-levels-of-hyperemesis-gravidarum/

Full history & examination with assessment of the degree of dehydration were undertaken. Blood was taken for the following investigation in both groups: Full blood count, urine for ketone, Blood urea and nitrogen, serum electrolyte (sodium, and potassium), Thyroid function test (T_3, T_4, TSH), Liver function test (AST, ALT, total protein, and albumin), fasting blood sugar , CCK & Abdominal and pelvic ultrasound. Serum Cholecystokinin was measured using ELISA Kit, USCN Life Science Inc. (LoNo: L130531819). After 48 hours of admission and initiation of medical management, the response was assessed and the blood biochemistry, electrolyte, and urine analysis were repeated.

A pregnancy-unique quantification of emesis/nausea (PUQE) index has been proposed, validated, and recently slightly modified, but it is seldom used clinically. Management is based on clinical severity as well as a woman's perception of severity and desire for treatment ([12])So we divided the patients group according to the clinical presentation, percentage of the loss of weight, duration of the need to supportive treatment, and the response that achieved during the hospital course, we used the model posted by HER Foundation as a base for the classification (table 1).

Statistical Packing for Social Science (SPSS) version 20 was used for statistical analysis. The categorical data presented as frequency and percentages tables. The continuous variables were presented as a mean & standard deviation. The Student's t–test (parametric) was used for group comparison to assess the significance of differences between the continuous variables. The correlation was assessed using Pearson or Spearman correlation coefficient along with related p-values. Shapiro-Wilk test was used to clarify that the sample of the study came from a normally distributed population.The level of significance in this study was of P-value less than 0.05.

RESULTS:

Table (2) shows the Demographic and obstetric data of the hyperemesis gravidarum and control groups. There were no significant difference in the mean age, & body mass indices between the two groups. Meanwhile, the gravidity for women with hyperemesis gravidarum was shown to be significantly higher than that of the normal group (p=0.01), Also that hemoglobin, WBC, platelet, total protein, albumin, liver transaminases (aspartate aminotransferase, AST, alanine aminotransferase ALT) were within normal ranges

Table 2: Demographic, obstetric, biochemical characteristics of study groups

Parameters	Normal pregnancy	Hyperemesis gravidarum	P-value
Number	30	30	-
Age (years)	30.3 ± 7.05	27.9 ± 7.3	0.206
BMI (kg/m^2)	26.3 ± 4.1	26.9 ± 4.2	0.587
Gestational age(week)	12.0 ±2.7	11.9 ±3.6	0.968
Gravida	2.5 ± 1.01	3.67 ± 2.19	0.01*
Hemoglobin (g/dl)	13.4 ± 1.6	12.7 ± 1.2	0.056
WBC (10^3/uL)	8.648 ± 1.690	8674 ± 2206	0.953
Platelet (10^3/uL)	252.422 ± 58.920	255.064 ± 80.624	0.929
Total protein (g/dL)	7.17 ± 0.35	7.25 ± 0.45	0.439
Albumin (g/dL)	4.21 ± 0.32	5.3 ± 6.38	0.354
AST (IU/L)	15.2 ± 3.47	17.17 ± 7.89	0.216
ALT (IU/L)	13.33 ± 9.57	18.33 ± 15.54	0.14
βHCG(mIU/ml)	83.6±6.5	101.67±7.1	0.000
TSH (uIU/ml)	1.73 ± 0.99	1.18 ± 1.01	**0.031***
$T4_{(free)}$ (ng/dL)	1.14 ± 0.17	1.35 ± 0.46	**0.012***
$T3_{(free)}$ (pg/mL)	3.22 ± 0.42	3.33 ± 0.5	0.225
FBG (mg/dL)	91.15 ± 11.04	92.83 ± 12.08	0.577
Blood urea nitrogen (mg/dL)	17.6 ± 4.79	23.9 ± 15.9	**0.042***
Serum Creatinine (mg/dL)	0.57 ± 0.11	0.53 ± 0.09	0.104
Sodium (mEq/L)	139.77 ± 3.64	137.73 ± 2.84	**0.019***
Potassium (mEq/L)	3.95 ± 0.24	3.79 ± 0.35	**0.042***
Serum Cholecystokinin (pg/ml)	63.98±37.84	34.03±17.48	**<0.001***

Table 3: Correlation coefficients between hormones within study sample

Parameters	*S. Cholecystokinin (pg/ml)*		*β-HCG (uIU/ml)*	
	Correlation coefficient (r)	*p-value*	*Correlation coefficient (r)*	*p-value*
β-HCG (uIU/ml)[a]	0.289	**0.044***	1	-
TSH (uIU/ml) [b]	0.362	**0.015***	0.265	**0.045***
S. Cholecystokinin (pg/ml)	1	-	0.289	**0.044***

[a] Pearson correlation coefficient, [b] Spearman correlation coefficient

Table 4: comparison of demographic, obstetrical, biochemical characteristic between moderate and severe hyperemesis gravidarum in patients

Parameters	**Moderate HG**	**Severe HG**	**P-value**
Number	20	10	-
Age (years)	26.3±6.4	29.1±9.6	**0.348**
BMI (kg/m^2)	28.2±4.6	26.5±3.5	**0.314**
Gestational age(week)	12.3±2.4	11.2±4.1	**0.360**
Hemoglobin (g/dl)	13.1 ± 1.1	12.4 ± 1.3	**0.023***
WBC (10^3/uL)	8.610 ± 1.340	9.174 ± 2.312	**0.009***
Platelet (10^3/uL)	256.422 ± 51.220	262.064 ± 78.624	**0.017***
Total protein (g/dL)	7.2 ± 0.3	7.6 ± 0.5	**0.01***
Albumin (g/dL)	4.5 ± 3.11	8.3 ± 4.08	**0.008***
AST (IU/L)	15 ± 5.2	19 ± 4.1	**0.042***
ALT (IU/L)	17.2 ± 9.57	27.1 ± 10.5	**0.015***
β-HCG (mIU/ml)	96 ± 6.8	113 ± 9	**<0.001***
TSH (uIU/ml)	2.4 ± 0.7	1.8 ± 0.5	**0.023***
$T4_{(free)}$ (ng/dL)	1.11 ± 0.3	1.4 ± 0.46	**0.046***
$T3_{(free)}$ (pg/mL)	3.25 ± 0.4	3.6 ± 0.4	**0.032***
FBG (mg/dL)	93.5 ± 9	86 ± 8.5	**0.037***
Blood urea nitrogen (mg/dL)	20.5 ± 8.79	28.4 ± 10	**0.035***
Serum Creatinine (mg/dL)	0.55 ± 0.09	0.47 ± 0.06	**0.017***
Sodium (mEq/L)	138 ± 2.2	136 ± 1.7	**0.019***
Potassium (mEq/L)	3.8 ± 0.2	3.5 ± 0.4	**0.01***
Serum Cholecystokinin (pg/ml)	39.8 ± 13.9	28.7 ± 11	**0.036***

There was a direct significant correlation between β-HCG with both S. Cholecystokinin and TSH, and between Cholecystokinin with TSH as illustrated in table 3.

In both groups, the free tri-iodothyronine (T_3) levels were within a normal level and there were no significant differences between the two groups, while the free thyroxine (T_4) levels were significantly higher in patients with hyperemesis gravidarum in comparison to the normal women. on the other hand; thyroid- stimulating hormone (TSH) levels were significantly lower in patients with hyperemesis, as shown in table two. The fasting blood sugar and serum creatinine levels showed no significant changes in both groups. The blood urea nitrogen showed a significant increase in women with hyperemesis in comparison to the normal one.The serum electrolyte levels in the form of sodium and potassium showed a significant decrease in women with hyperemesis in comparison to the normal group.

The mean serum levels of cholecystokinin CCK were significantly lower in hyperemesis gravidarum women in comparison with normal pregnancy group, as p-value show less than 0.001.

Regarding the classification of the patient group according to the severity, we had two subgroups, 20 patients with moderate severity, while 10 patients with a severe degree of hyperemesis gravidarum. Table 4, shows the comparison between the two subgroups regarding the demographic and obstetrical characteristic. There was no significant difference between the two subgroups. Also, table 4 shows significant differences in almost all the hematological, biochemical, and hormonal parameters that had been evaluated in this study, all go with the severity of the condition. The cholecystokinin is lower in severe cases than moderate cases (28.7 ± 11vs. 39.8 ± 13.9; P=0.036). The β-HCG is significantly higher in patients with severe cases than moderate cases.

DISCUSSION

It is commonly believed that HG is usually self-limited disorder, but if we return back before the administration of intravenous fluid, the mortality from HG was 159 deaths / million births in the UK.[11] Even in the current state the complications of HG is worrisome for the maternal health and the outcome of pregnancy.

The strategy for the management of any condition depends on proper understanding of the underlying pathophysiology. Verberg *et al* had conducted a literature review from 1966 to 2005 to make a summary of the causes and pathophysiology of HG, the possible role of progesterone, estrogen, and HCG has been largely evaluated, however, many other hormones such as leptin, placental growth hormone, prolactin, thyroid and adrenal cortical hormones have been studied. In addition, evidence considering infectious, immunological, psychological, metabolic and anatomical causes for HG had been tested in that study. This study highlighted the need for more wide studies declaiming the pathogenesis and etiology of HG and in one statement this review stated that the cause of HG is unknown[11]

During pregnancy, sex steroids effect gastric and colonic smooth muscle in the form of slowing in it transit times and gastric emptying that may cause nausea. Many authors tried

to measure gastric emptying in HG patients, and in contrast to the expected finding, they noticed an increase in gastric emptying.[13, 14]

Gastrointestinal CCK decreases gastric emptying, alter gastric sensory function and in critically ill patients, the gastric empty was delayed in 64% of patients, while the baseline CCK was high in comparison with the control.[15] This observation is on the contrary to a study published recently by Ebru Biberoglu et al where they demonstrated that the CCK is halved in pregnant patients with severe HG in comparison with normal pregnant ladies.[16]Our study demonstrates the same finding where the level is low in pregnant ladies with HG. The usual observation that most patients with severe HG showed response after admission to the hospital when they stopped oral intake and depended on intravenous fluid, but resume vomiting when they restart eating, this observation could be explained by local reflex mediated by CCK which mediates the delay in gastric empty, and the relaxation of gastro-esophageal junction end in vomiting. This explanation is `supported by the findings that CCK1 antagonists have accelerated the gastric empty and block the CCK induced delay in gastric empty[17].

This study also has demonstrated the significant difference in the level of CCK between two different groups in severity of HG, this finding made us search to find same result or explanation to this finding, but we failed to find that. So this finding would be considered as supportive evidence to the finding above i.e. low level of CCK in HG, and we recommend further study in this field to evaluate the role of serum cholecystokinin as a marker of severity of hyperemesis gravidarum.

The review of the literature does not support strongly the hypothesis that HG and gastrointestinal motility are related, so whether this finding is a result rather than the causal relationship is a reasonable question. But the finding of high level of CCK in critically ill patients with a delay in gastric empty, and our finding of low level in HG, where the gastric empty is increased, may increase the suspicion of a causal relationship between CCK and HG, yet the cause of this low level of CCK is not understood.

The finding of high T_4 and low TSH are in accordance with medical literature where we can find a third of HG patients have transient thyrotoxicosis, and this may be explained by the thyrotrophic effect of HCG.[18]

There was a direct correlation between the CCK and other factors like TSH, and β-HCG that support our theory. Still, the clinical practice depends on the treatment of HG on supportive treatment without definitive line of treatment. So more work and research to explore the underlying pathophysiology of HG.

CONCLUSION

Maternal serum cholecystokinin level was significantly reduced in pregnant women with hyperemesis gravidarum in comparison to the healthy uncomplicated pregnant women. This reduction is inversely correlated with the severity of the condition. This relationship with the severity triggers the need for further studies to evaluate the role of cholecystokinin as a marker of severity of hyperemesis gravidarum rather than a causal relationship.

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