

## A Study of thyroid status in women with Hyperemesis gravidarum

Ahmed Ragab MSC, Abdelmoniem Zakaria. MD, Sameh Saied. MD, Ahmed Raafat. MD

Department of Obstetric and Gynecology, Faculty of Medicine, Al Azhar University, Egypt  
[docmedo86@yahoo.com](mailto:docmedo86@yahoo.com)

**Abstract: Background:** Hyperemesis gravidarum may cause volume depletion, electrolytes and acid-base imbalances, nutritional deficiencies, and even death. Severe hyperemesis requiring hospital admission occurs in 0.3-2% of pregnancies. Endocrine abnormalities in hyperemesis gravidarum have been postulated and evidence presented. **Methods:** The study will be conducted on 50 pregnant women at 6-14 week of gestation, The so pregnant women will be divided into two groups. Group (1): including 25 cases with exercise vomiting admitted to the ward. i.e (study group). Group (2): including 25 women with normal. i.e (controlled group). **Conclusion:** From the results of the present study. It can be concluded that in clinically euthyroid hyperemetic women, gestational transient thyrotoxicosis may be the cause of the condition and may attribute to its prolongation to second trimester. [Ahmed Ragab, Abdelmoniem Zakaria, Sameh Saied, Ahmed Raafat. **A Study of thyroid status in women with Hyperemesis gravidarum.** *N Y Sci J* 2017;10(9):13-22]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 2. doi: [10.7537/marsnys100917.02](https://doi.org/10.7537/marsnys100917.02).

**Keywords:** vomiting in pregnancy, Hyperemesis gravidarum, thyroid disease

### 1. Introduction

Nausea and vomiting affects up to 85% of pregnant women. Although popularly known as 'morning sickness' one study demonstrated that less than 20% of women experienced nausea only in the morning and 80% reported nausea throughout the day. The condition is usually mild and self limiting, peaking at around 9 weeks gestation and usually resolving, frequently quite abruptly, before 14 weeks gestation (1).

Hyperemesis gravidarum (HG) is characterized by persistent nausea and vomiting associated with ketosis and weight loss (>5% of prepregnancy weight). Hyperemesis gravidarum may cause volume depletion, electrolytes and acid-base imbalances, nutritional deficiencies, and even death. Severe hyperemesis requiring hospital admission occurs in 0.3-2% of pregnancies (2).

Hyperemesis gravidarum was the most common indication for admission to the hospital during the first part of pregnancy and was second only to preterm labor as the most common reason for hospitalization during pregnancy in the Western world (3).

A number of risk factors associated with hyperemesis have been reported, including primigravida, low maternal age, multiple gestation, fetal anomalies, a previous pregnancy complicated by hyperemesis, female sex, psychiatric conditions, and both high and low maternal prepregnancy weight. Smoking, on the other hand, has been associated with a reduced risk of hyperemesis (4).

Its etiology is obscure. Factors responsible for it vary from social, psychological, allergy to products produced by ovum to dietary deficiency of protein, vitamin B1 and B6. It has also been related to high or

rapidly rising levels of chorionic gonadotrophins or its effect on steroidogenesis causing increased estradiol concentration or lower body mass index (BMI). Human chorionic gonadotropin (hCG) was even thought to be indirectly involved in its etiology by its ability to stimulate thyroid and molecular variants of hCG with greater thyrotrophic activity have been documented in hyperemetic pregnant women, even biochemical thyrotoxicosis has been displayed in these women (5).

Hyperemesis gravidarum has been associated with increases in maternal adverse effects, including splenic avulsion, esophageal rupture, Mallory-Weiss tears, pneumothorax, peripheral neuropathy, and preeclampsia, as well as increases in fetal growth restriction and mortality (6). Before the introduction of intravenous (i.v.) rehydration, the mortality from hyperemesis was considerable, the most well known case probably being that of Charlotte Bronte who died in 1855 from severe nausea and vomiting 4 months into her pregnancy. Four cases have been reported in the literature with advanced vitamin and metabolite disturbances such as Wernicke encephalopathy, coagulopathy and peripheral neuropathy (7).

Various therapies have been used to treat nausea and vomiting during pregnancy. Initial treatment is supportive, with attention focused on the avoidance of foods associated with nausea. Frequent small meals are often recommended. With increasing maternal symptomatology, antiemetic pharmacologic therapy can be instituted. For patients that fail outpatient management, fluid and electrolyte replacement and supplemental nutrition may be used, sometimes requiring multiple hospitalizations (8).

Thyroid function test values change in gestation, especially within the first trimester, largely because of estrogen-induced increases in serum thyroxine-binding globulin (TBG) levels and hCG –induced increases in thyroid hormone synthesis and release (9).

Gestational transient thyrotoxicosis (GTT) occurs on early pregnancy and is reported to have strong association with hyperemesis gravidarum (10).

## 2. Patients and Methods

This prospective cross-sectional study has been carried out in Al Husien university Hospital. The study was conducted on 100 pregnant women at 6-14 weeks of gestation; out of these 50 women with excessive vomiting admitted in ward have constituted study group however, 50 women with normal pregnancy presented in the out-patient clinic have formed control group. The study was carried during the period from janury 2015 to june 2016.

### Sample size calculation:-

Based on a previous study of Gill et al. (2007), sample size calculation formely was advised by Research Ethics Committee, Ain Shams University. It was done with Stata Version 10.0, based on a 0.05 power 0.8:-

Estimated sample size for two-sample comparison of proportions Test Ho:  $p_1=p_2$ , where  $p_1$  is the proportion in population 1 and  $p_2$  is the proportion in population 2.

### Assumptions:

Alpha=0.0100 (two sided)

Power=0.9000

$P_1=0.6700$  (prevalence of increase T4 in study group)

$P_2=1600$  (prevalence of increase T4 in control group)

$n_2/n_1 = 1.00$

Estimated required sample size:

$n_1 = 30$

$n_2 = 30$

The required sample size was 30 in each group with a total of 60 ladies. However, for approval of the protocol by the ethical committee of the Obstetrics and Gynecology Department, sample size has been enlarged to include 50 patient in each group with a total of 100 ladies.

The protocol was approved by the ethical committee of the Obstetrics and Gynecology Department, Ain Shams University in September 2010.

*All members involved in this study fulfilled the following inclusion criteria, and exclusion criteria:*

### Inclusion criteria:-

- Age: 16-38 years.
- Gravidity: only primigravidae.

- BMI (kilograms per square meter): (20-24.9 kg/m<sup>2</sup>) which corresponds to ideal weight category (Cedergren et al., 2008).

- An ultrasonographic documentation of a singleton, viable intrauterine pregnancy with a gestational age ranging from 6-14 weeks.

### Exclusion criteria:-

- Women with indications for thyroid testing in pregnancy; family history of autoimmune thyroid disease, women on thyroid hormone therapy, presence of goiter, type 1 diabetes mellitus, and previous history of high-dose neck radiation, therapy for hyperthyroidism (Mestman et al., 1999).

- Women with an elevated hCG and hyperthyroidism in pregnancy due to gestational trophoblastic diseases, or multiple pregnancy.

- Nonpregnancy-related causes of persistent vomiting due to medical or surgical disorders eg., gastrointestinal, genitourinary, metabolic and neurological disorders.

- Any cause affecting estradiol level eg., intrauterine growth restriction and hyperplacentalosis as in DM and Rh isoimmunization.

*Women included in this study were subjected to the following:-*

**A. Verbal consent:-** obtained after explaining the aim of the research for every woman.

### B. Full History taking:-

#### (1) Personal history:

- Name.
- Age.
- Duration of marriage.
- Living offsprings.
- Special habits eg., smoking.
- Urban-rural classification of residence.
- Social class.
- Occupation of woman and her husband.

#### (2) Obstetric history:

- Gravidity-Parity.
- Date of last menstrual period.
- Gestational age.
- Drug intake during current pregnancy.

#### (3) Menstrual history:

- Amount.
- Duration.
- Frequency.
- Dysmenorrhea.
- Date of last menstrual period.

#### (4) Contraceptive history:

Past use of oral contraceptives, and response to oral contraceptives used.

#### (5) Past history:

- Medical disorders eg, hyperthyroid disorders, diabetes mellitus, respiratory disorders, psychiatric disorder, endocrine disorders....etc.

- Medications.
- Allergies, and adverse drug reactions.

**(6) Family history****(7) Present history:**

The time, onset, severity, pattern, and alleviating and exacerbating factors (e.g. relationship to meals, medications, prenatal vitamins, stress, other triggers). A thorough review of systems for any symptoms that might suggest other gastrointestinal, renal, endocrine, and central nervous system disorders.

*Ladies out of the inclusion criteria were excluded from the study.*

*Similarly ladies were excluded if they had one or more of the exclusion criteria.*

**C. Clinical Examination:-****(1) General examination:**

Attention has been paid to the vital signs, including standing and lying blood pressure and pulse, volume status (eg, mucous membrane condition, skin turgor, neck veins, mental status), general appearance (eg., nutrition, weight, height, BMI), and thyroid examination findings.

**(2) Abdominal examination:**

Attention has been paid to fundal level, abdominal swelling, tenderness, surgical scars, and hernias.

**(3) Ophthalmological examination** for visual acuity, confrontation visual fields, extraocular movements, papillary tests, slit lamp examination for anterior and posterior segments and dilated fundus examination for vitreous, optic nerve, blood vessels, macula and retina.

**D. Investigations:-****(1) Laboratory investigations:**

The following investigations were done in the patient group as routine investigations:

- Complete Blood count.
- Serum electrolytes.
- Liver function tests.
- Kidney function tests.
- Random blood sugar.
- INR.
- Urine examination especially for ketone bodies and for exclusion of urinary tract infections.

**(2) Ultrasonographic examination:**

To confirm gestational age and to rule out trophoblastic disease and multiple pregnancy.

**E. Evaluation of thyroid status through measurement of serum Total T4 (TT4), total (T3) TT3 (with adjusted reference range levels for pregnancy) and TSH levels:-**

This has been done for all members involved in the study who fulfilled the inclusion criteria, and exclusion criteria.

The most accurate and direct measurements of the concentrations of free T4 and free T3 in serum are

performed by assay of these hormones in a dialysate or ultrafiltrate of serum. This is not practical for clinical purposes and alternative strategies have been developed to estimate free thyroid hormone concentrations (**Larsen et al., 2008**).

Adjusting the TT4 in pregnancy by a factor of 1.5 compared with nonpregnant reference ranges yields a workable estimate of FT4. Since TT4 is an inexpensive assay well suited to automation, the simple adjustment described above would provide clinicians with an inexpensive and readily available method for estimating free thyroxine (**Lee et al., 2009**).

**Specimen collection and preparation:**

In women of both groups 5 ml of venous blood was withdrawn and the serum was separated (within 30 minutes) by centrifugation for 10 minutes, and stored at -20 C° till the time of assay. Storage was done in Medical Research Center, Ain Shams University.

Serum total T4, total T3 and TSH levels have been measured by radioimmune assay technique in Medical Research Center, Ain Shams University. It has been done through the following kits:

1) The Calbiotech, Inc. (CBI) TSH ELISA Kit for the quantitative measurement of TSH in human serum. It belongs to *Calbiotech Inc., 10461 Austin Dr, Spring Valley, CA, 91978, USA*.

2) The Immunospec T3 EIA for the quantitative measurement of total Triiodothyronine (TT3) in human serum. it belongs to Immunospec Corporation, 7018 Owens mouth Ave. Suite 103, Canoga Park, CA, 91303, USA.

3) The Immunospec T4 EIA for the quantitative measurement of total Tetraiodothyronine (TT4) in human serum. it belongs to Immunospec Corporation, 7018 Owensmouth Ave. Suite 103, Canoga Park, CA, 91303, USA.

**Statistical analysis:**

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, Kruskal-Wallis and Analysis of variance [ANOVA] and Mann-Whitney tests by SPSS V17.

$$\frac{\sum x}{n}$$

$$1. \text{ Mean} = \frac{\sum x}{n}$$

Where  $\sum$  = sum & n = number of observations.

$$2. \text{ Standard Deviation [SD]:}$$

$$SD = \sqrt{\frac{\sum |x - \bar{x}|^2}{n - 1}}$$

Standard Error [SE]:

$$SE = \frac{SD}{\sqrt{n}}$$

**Analysis of variance [ANOVA] tests.**

According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

**Kruskal-Wallis**

A nonparametric equivalent to one-way ANOVA. Tests whether several independent samples are from the same population. Assumes that the underlying variable has a continuous distribution, and requires an ordinal level of measurement.

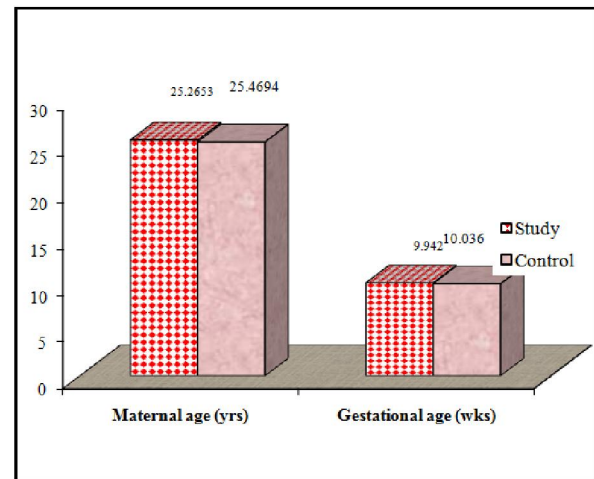
**Mann-Whitney**

A nonparametric equivalent to the t test. Tests whether two independent samples are from the same population. It is more powerful than the median test since it uses the ranks of the cases. Requires an ordinal level of measurement. U is the number of times a value in the first group precedes a value in the second group, when values are sorted in ascending order.

- P value >0.05      Non significant (NS)
- P<0.05              Significant (S)
- P<0.001            High significant (HS)

**3. Results**

This prospective cross-sectional study has been carried out in Al Husien university Hospital during the period from January 2015 to June 2016. The study was conducted on 100 pregnant women at 6-14 weeks of gestation; out of these 50 women with excessive vomiting admitted in ward have constituted study group however, 50 women with normal pregnancy presented in the out-patient clinic have formed control group.



**Fig. (1):** Comparison between the studied groups as regard maternal age (years) and gestational age (weeks)

**Table (5):** Demographic data of ladies involved in the study

Characteristics	Study (n=50) Mean ±SD	Control (n=50) Mean ±SD	Mann-Whitney test		
			Z	P-value	Sig.
Maternal age (yrs)	25.4694 ±3.62918	25.265 ±3.68429	-0.261	0.794	NS
Gestational age (wks)	10.0360 ±2.22084	9.9420 ±2.0875	-0.190	0.850	NS

\*\* Significant p <0.05

This table shows no significant difference between the studied groups as regard maternal age, and calculated gestational age by using the Mann-Whitney u test.

**Table (1):** Frequency of HG symptoms in study group

Symptoms	No. of patients	Percentage
Nausea > 6 hrs/24 hr	50	100%
Retching episodes > 7 times / 24 hrs	50	100%
Vomiting episodes > 4 attacks / 24 hrs	50	100%
Fatigue	50	100%
Weight loss	50	100%
Dizziness	50	100%
Decreased concentration	10	20%
Psychological symptoms	50	100%
Sleep disturbance	20	40%

**Table (2):** Frequency of HG complications in study group

Complications	No. of patients	Percentage
Dehydration at time of examination	26	52%
Marked weight loss	50	100
Severe psychological upset	32	64%
Need for psychiatric consultation	1	2%
Wernicke's encephalopathy	0	0%
Abnormal fundus examination	0	0%
Splenic avulsion	0	0%
Pneumothorax	0	0%
Acute pancreatitis	0	0%
Diagnosed venous thromboembolism	0	0%
Haematemesis	2	4%
Laryngitis	1	2%
Fainting attacks	18	36%
Extended course beyond GA 14 wks	5	10%
Acid – base imbalance	?	?
Admission to ICU	2	4%
Death	0	0%
Abortion	0	0%
Ketonuria	50	100%
Specific gravity of urine > 1025	32	64%
Elevated serum bilirubin	3	6%
Elevated ALT	19	38%
Hypokalaemia	28	56%
Hyponatraemia	21	42%
Elevated serum creatinine	1	2%
Others:		
Decreased haemoglobin	37 out of 47 patients	
Elevated HCT	1 out of 42 patients	
Elevated AST	18 out of 43 patients	

**N.B:**

- Abnormalities in laboratory investigations were described according to normal ranges supplied by laboratories of the two hospitals where the study has been conducted.
- Test results for INR, and arterial blood gases were not available for most of the patients.

**Table (3):** Lines of treatment of HG provided for study group

Line of treatment	No. of patients	Percentage
Intravenous fluids	50	100%
Metoclopramide	50	100%
Cortigen B6	50	100%
Meclizine hydrochloride 50 mg	50	100%
Ondansetron	9	18%
Hydrocortisone	3	6%
Diet modification	50	100%
Emotional support	?	?
Alternative therapies	0	0%
Ranitidine	50	100%
Vitamins (B1, B6, B12)	50	100%
Parental potassium	8	16%
Low molecular weight heparin (subcutaneous)	9	18%
Total parental nutrition	0	0%
Antithyroid drugs	0	0%
Therapeutic abortion	0	0%



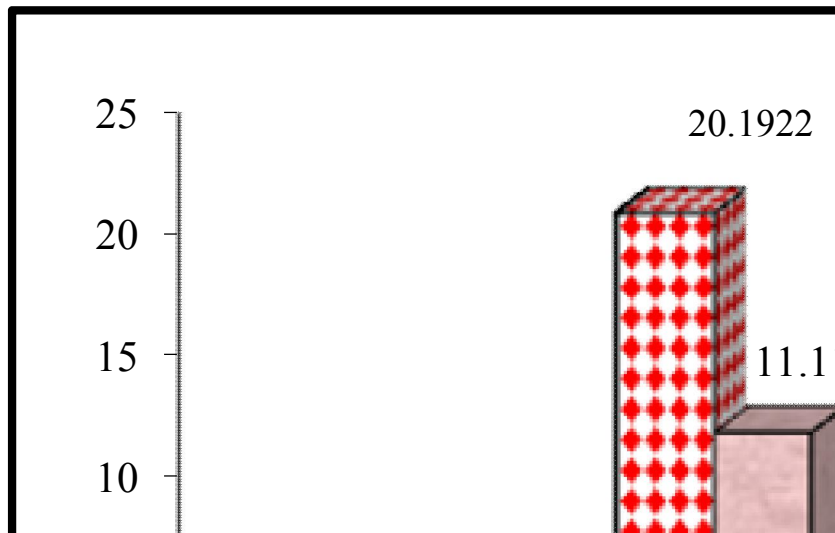
**Table (4):** Comparison between the studied groups as regard TT3, TT4, and TSH levels.

Variable	Study (n=50) Mean ±SD	Control (n=50) Mean ±SD	Mann-Whitney test		
			Z	P-value	Sig.
TT3	2.1873±1.40610	1.7550±0.91574	-1.138	0.255	NS
TT4	20.1922±6.05258	11.1130±3.76418	-6.818	0.0001	HS
TSH	1.0138±0.40550	1.4460± 0.60494	-3.641	0.0001	HS

\*\* Significant  $p < 0.05$

This table shows highly significant difference between the studied groups as regard TT4, being significantly higher in case group. Also, it shows highly significant difference between the studied

groups as regard TSH, being significantly lower in case group. TT3 while being higher in case group, however the difference is not significant. Analyses were done using the Mann-Whitney u test.



**Fig. (2):** Comparison between the studied groups as regard mean TT3 levels (ng/ml), mean TT4 levels (µg/dl) and mean TSH levels (µIU/ml).

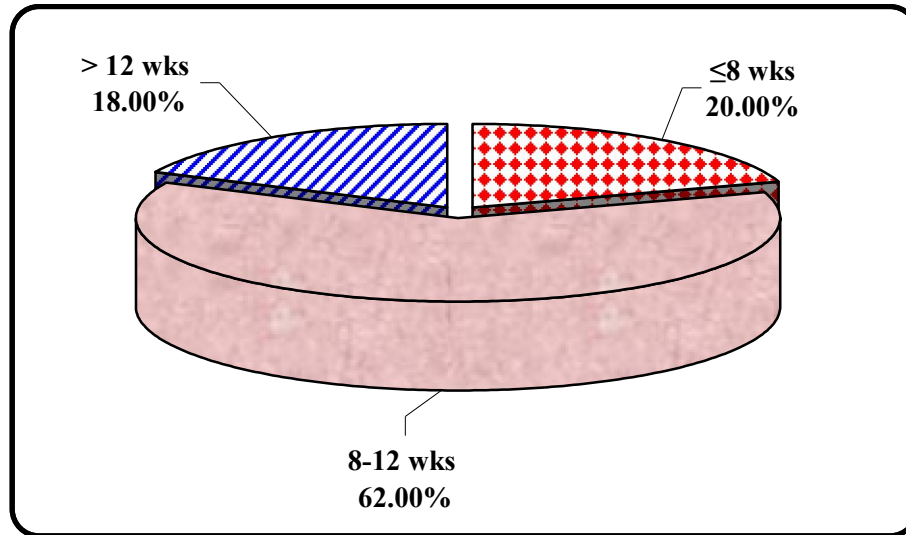
**Table (5):** Correlation between gestational age and thyroid profile in case group

Variable	Gestational age in weeks (wks)			ANOVA		
	< 8 wks (n=10) Mean ± SD	8-12wks (n=31) Mean ± SD	> 12 wks (n=9) Mean ± SD	f	P-value	Sig.
TT3	1.3790±0.85209	2.4977±1.54623	2.0644±1.27883	2.483	0.094	NS
TT4	14.9960±6.09369	20.2303±6.78690	17.4111±7.20841	2.477	0.095	NS
TSH	1.3670±0.50752	0.9830±0.50016	1.1300±0.46306	2.314	0.110	NS

\*\* Significant  $p < 0.05$

This table shows that the highest mean TT3 and the highest mean TT4 are at gestational ages more than 8 weeks but not more than 12 weeks and the lowest mean values for both hormones are at gestational ages 8 weeks or less. However, no significant correlation could be detected between gestational age versus TT3, TT4. The table also shows

that, the lowest mean TSH is at gestational ages more than 8 weeks but not more than 12 weeks and the highest mean value for it is at gestational ages 8 weeks or less. However, no significant correlation could be detected between gestational age versus TSH. Analyses were done using the ANOVA test.



**Fig. (3):** Distribution of cases according to gestational age.

#### 4. Discussion

Hyperemesis gravidarum is defined as excessive vomiting during pregnancy, which may lead to severe outcomes including weight loss, dehydration, fasting acidosis, alkalosis due to hydrochloric acid loss, and hypokalemia (11). Both the etiology and pathogenesis of hyperemesis gravidarum remain unknown (12). It may become so severe as to require hospitalization and termination of pregnancy. Endocrine abnormalities in hyperemesis gravidarum have been postulated and evidence presented. In view of the structural similarities between human chorionic gonadotropin and thyroid stimulating hormone, links between hCG, and thyroid stimulation have been proposed. However, there remains controversy concerning the pathogenic role of the thyroid axis in hyperemesis gravidarum and morning sickness (13).

This study aimed to evaluate thyroid status in women with hyperemesis gravidarum. This prospective cross-sectional study has been carried out in Ain Shams Maternity Hospital and Mataria Teaching Hospital during the period from October 2010 to April 2011. The study was conducted on 100 Egyptian primigravidae at 6-14 weeks of gestation; out of these 50 ketonuric (1+ or more) women with excessive vomiting admitted in ward have constituted study group however, 50 women with normal pregnancy presented in the out-patient clinic have formed control group.

The current study showed no significant difference between the studied groups as regard maternal age, and gestational age. (14) found that maternal age was significantly different between the hyperemetic (n=58) and control (n=58) groups.

The present study revealed that 20% of HG patients were pregnant 8 weeks or less, 62% from 8-

12 weeks and, 18% more than 12 weeks. Mean T3 and mean T4 showed non significant trend to correlate with GA with p value 0.094 and 0.095 respectively. The same was observed as regard mean TSH (p value = 0.110). Mean T3 and mean T4 at GA 8-12 weeks were the highest, with the lowest corresponding mean values at GA up to 8 weeks. On the other hand, mean TSH at GA 8-12 weeks was the lowest, with the highest corresponding mean value at GA up to 8 weeks.

found that 82% women had vomiting at less than 12 weeks of gestation that coincides with the period of peak hCG levels. Similarly, (15) found the peak incidence of hyperemesis gravidarum to correspond with the peak titre of beta-subunit of human chorionic gonadotropin ( $\beta$ hCG) which is usually at about 8–10 weeks of gestation (16) also reported vomiting in 93.3% of women at less than 12 weeks of gestation.

In the present study, all the ladies were free of thyrotoxic manifestations. However, on analyzing thyroid functions, serum TT3 levels were increased (> adjusted level for pregnancy which is 0.9-3 ng/ml) in significant number of hyperemetic women (32% vs 12%). However increase in mean T3 level ( $2.1873 \pm 1.40610$  vs  $1.755 \pm 0.91574$  ng/ml) was not statistically significant ( $p > 0.05$ ). TT3 was found to less than 0.9 ng/ml in 10% of hyperemetic women versus 16% of control. 56% of hyperemetic women as compared to only 4 % of normal pregnant women were found to have raised serum TT4 level (> adjusted level for pregnancy which is 7.5-19.5  $\mu$ g/dl). Mean T4 level was significantly higher ( $20.1922 \pm 6.05258$  vs  $11.113 \pm 3.76418$   $\mu$ g/dl) in study group ( $p < 0.001$ ). TT4 was not found to be less than 7.5  $\mu$ g/dl in any hyperemetic woman however, this occurred in 18% of control women. Mean TSH level was

significantly lower ( $1.0138 \pm 0.40550$  vs  $1.446 \pm 0.60494$   $\mu\text{IU/ml}$ ) in study group ( $p < 0.001$ ). Serum TSH level was less than normal ( $< 0.4$ – $4.2$   $\mu\text{IU/ml}$ ) in 6 % women of study group whereas in control group only 2 % had TSH less than normal. TSH levels from  $0.4$   $\mu\text{IU/ml}$  to less than  $1$   $\mu\text{IU/ml}$  have been found in 38% of HG women compared to 24% of control group. TSH levels from  $1$   $\mu\text{IU/ml}$  to less than  $2$   $\mu\text{IU/ml}$  have been found in 50% of HG women compared to 48% of control group. TSH levels of  $2$   $\mu\text{IU/ml}$  or more have been found in 6% of HG patients compared to 26% of control group. The present study found that the highest level for TSH in HG women as  $2.1$   $\mu\text{IU/ml}$  compared to  $3$   $\mu\text{IU/ml}$  in control women.

The present study was broadly consistent to the finding of who found that maternal age and all hormones (thyroid stimulating hormone, free thyroxine, free triiodothyronine and total beta human chorionic gonadotropin) were significantly different between the hyperemetic ( $n=58$ ) and control ( $n=58$ ) groups. However, logistic regression analysis demonstrated that only maternal age, free thyroxine and thyroid stimulating hormone were significant independent variables. Differences in maternal age and thyroid function are highly discriminatory with regard to hyperemesis gravidarum.

The results of the current study are in agreement with (15) in Kuwait. The hyperemesis gravidarum group ( $n=50$ , with ketonuria 3+ or more on dip stick examination) had significantly higher hormone titres with TT4  $11.1 \pm 3.66$  versus  $9.21 \pm 2.30$   $\mu\text{g/dl}$ ,  $p < 0.004$  and FT4  $1.45 \pm 0.39$  compared to  $1.28 \pm 0.23$ ,  $p < 0.01$  respectively. Conversely, the TSH levels were significantly lower in the study than in the control group ( $n=50$ );  $0.34$  compared to  $1.74$   $\text{mIU/ml}$ ,  $p < 0.0001$ . In spite of these significant differences the results of the TT4 and FT4 hormone titers in both the study and control groups, were within the normal range and TSH less than normal range in the study group. There was a strong positive correlation between the  $\beta\text{hCG}$  titre and the incidence of hyperemesis gravidarum. Furthermore, there was a strong correlation between TT4 and incidence of hyperemesis gravidarum. This strongly suggests a stimulatory effect on the thyroid gland, traceable to elevated  $\beta\text{hCG}$  in the study population. This is in agreement with reports that  $\beta\text{hCG}$  has a thyrotrophic effect in humans (17).

The finding of (15) is in contrast to report from Hong Kong (18) and (19), which showed that Asian women are at increased risk of developing gestational thyrotoxicosis in association with hyperemesis gravidarum. (15) attributed the high incidence of hyperemesis gravidarum in Kuwaitis to the strong family influences in the Arab community (20). This is

in accordance with the reports that hyperemesis gravidarum is associated with legal pregnancy, low maternal age, primigravidity and high maternal weight (21).

In this regard difference in economic status between Egypt and Kuwait should be considered. More over, in contrast to (15), in the present study all participants were primigravidae with younger mean age values and, the GA did not exceed 14 weeks. Its to be note that thyroid microsomal antibodies were measured to identify and exclude those with thyroid disorder in (15) which was not available in the present study.

The results of the current study could agree with (18) in Japan. It showed that serum free T4 and free T3 were higher in the hyperemesis group ( $P < 0.01$ ) and the emesis group ( $P < 0.01$ ), and serum TSH was suppressed to less than  $0.1$   $\text{mIU/l}$  in both groups. Two of eight women with hyperemesis, who had the highest free T4 and thyroid-stimulating activity/hCG ratio, showed overt clinical symptoms of thyrotoxicosis; all the symptoms disappeared in association with a fall in thyroid-stimulating activity and free T4.

In the present study however, overt clinical symptoms of thyrotoxicosis was a reason to exclude the patient from the study.

The results of the present could agree with (13), a study from Japan. They found that all the thyroid hormones (rT3, FT3, FT4), non esterified fatty acids (NEFAs) and weight loss were significantly higher in hyperemesis gravidarum ( $n=80$ ) than in control subjects ( $n=30$ ), and also higher than in those with milder symptoms of morning sickness ( $n=30$ ) ( $p < 0.05$ ). Patients with morning sickness also showed chemical evidence of hyperthyroidism when compared with control subjects ( $p < 0.01$ ). Elevations of FT3, FT4 and NEFAs correlated with the extent of weight loss, the latter taken as the index of the severity of hyperemesis gravidarum ( $p < 0.05$ ). Only rT3 correlated with both weight loss and the rate of lipolysis, as reflected by elevations of NEFAs ( $p < 0.05$ ).

A study from Turkey, (22) showed that mean serum hCG, free T3, and free T4 levels were significantly higher in hyperemesis gravidarum patients ( $n=24$ ) than in healthy controls ( $n=20$ ) ( $P < 0.007$ ).

In this study however, there was no statistically significant difference in terms of TSH in contrast to the current finding.

The results of the current study agree with (23) a study from Pakistan. It showed that serum T<sub>4</sub> and hCG levels were significantly increased in hyperemesis gravidarum while TSH demonstrated a significant decline in the same group.



The authors concluded that these variables are involved in the pathogenesis of morning sickness and hyperemesis gravidarum not only because their levels were significantly altered but the extent of increase or decrease in their level correlated well with the severity of symptoms in the study subjects.

The results of the present study agree with (24), a study conducted in Korea. In this study, it was found that a significant increase in serum total T4 ( $p < 0.001$ ) and T3 ( $p < 0.05$ ), and a significant decrease in serum TSH ( $p < 0.001$ ) were observed in pregnancy with hyperemesis gravidarum relative to the level in normal pregnancy. These results were correlated with the severity of nausea and vomiting.

The present study agrees with (5), a study conducted in India. On analyzing thyroid functions, serum T3 levels were increased i.e.  $>1.66\text{ng/ml}$  in significant number of hyperemetic women (22% vs 8%). However increase in mean T3 level ( $1.70 \pm 2.9$  vs  $1.24 \pm 0.35\text{ng/ml}$ ) was not statistically significant ( $p > 0.05$ ). 67% of hyperemetic women as compared to only 16% of normal pregnant women were found to have raised serum T4 level i.e.  $>12.00\text{ng/dl}$ . Mean T4 level was significantly higher ( $14.10 \pm 3.28$  vs  $9.89 \pm 2.46$  ng/dl) in study group ( $p < 0.001$ ). Serum TSH level was less than normal i.e.  $<0.47$  IU/ml, in 18% women of study group whereas in control group only 8% had TSH less than normal. Mean TSH level was significantly lower ( $1.70 \pm 1.16$  vs  $2.36 \pm 1.33$ ) in study group ( $p < 0.01$ ).

(5) did not use adjusted level for pregnancy as regard TT4 and TT3 so they did not find subnormal levels for such hormones in their study in comparison to the findings of the present study which rely on adjusted levels for pregnancy.

Mean values for TT4 and TT3 in the present study are higher than those in (5) and, this may be due to difference in kits used and some important differences in inclusion criteria between the two studies.

In contrast to (5) where only 53% and 42% of HG group ( $n=100$ ) and control ( $n=50$ ) were primigravidae respectively, all participants in the current study were primigravidae and, it's known that nulliparous women and women pregnant for the first time have higher levels of estrogen than other women (11).

Difference in distribution of women according to period of gestation and upper limit for gestational age between the current study and (5) could be another explanation where all participants in the present study are pregnant at not more than 14 weeks while, in (5) all women pregnant at less than 20 weeks were included. In normal pregnancy, hCG concentration peaks at weeks 8 to 12, with maximum levels of 30 to 100 U/mL. Thyroid-stimulating activity has also been

noted to correlate directly with the serum hCG level (25). (26) however, found that the peak  $\beta$ -hCG was at 12- 15 weeks gestation (mean 283, 136 mIU/ml) followed by a decline.

The degree of thyroid abnormalities is directly related to the severity of vomiting and weight loss in transient hyperthyroidism of HG (27). All HG patients in the present study were ketonuric and hospitalized however, (5) only 7% of HG patients were ketonuric moreover, only 37 % of HG patients in their study were hospitalized with severe illness.

## References

1. Sheehan P (2007): Hyperemesis gravidarum— Assessment and management. *Australian Family Physician*, 36 (9): 698-701.
2. Ogunyemi DA and Fong A (2009): Hyperemesis Gravidarum. *eMedicine Specialties > Obstetrics and Gynecology > General Obstetrics* <http://emedicine.com/med/topic1075.htm>.
3. Cedergren M, Brynhildsen J, Josefsson A, Sydsjö A and Sydsjö G (2008): Hyperemesis gravidarum that requires hospitalization and the use of antiemetic drugs in relation to maternal body composition. *Am J Obstet Gynecol*, 198:412.e1-412.e5.
4. Fell DB, Dodds L, Joseph KS, Allen VM and Butler B (2006): Risk factors for hyperemesis gravidarum requiring hospital admission during pregnancy. *Obstet Gynecol*, 107:277-84.
5. Gill BK, Jindal P, Kumar R, Tiwari S, Sharma N, et al. (2007): A study of thyroid status in hyperemesis gravidarum. *Indian Journal of Clinical Biochemistry*, 22 (1):148-151.
6. Quinlan JD and Hill DA (2003): Nausea and Vomiting of Pregnancy. *Am Fam Physician*, 68 (1):121-8.
7. Holmgren C, Aagaard-Tillery KM, Silver RM, Porter TF and Varner M (2008): Hyperemesis in pregnancy: An evaluation of treatment strategies with maternal and neonatal outcomes. *Am J Obstet Gynecol*, 198:56.e1-56.e4.
8. Pearce EN, Oken E, Gillman MW, Lee SL, Magnani B, et al. (2008): Association of first-trimester thyroid function test values with thyroperoxidase antibody status, smoking and multivitamin use. *Endocr Pract*, 14 (1): 33-39.
9. Albaar MT and Adam J MF (2009): Gestational transient thyrotoxicosis. *Acta Med Indones-Indones J Intern Med*, 41 (2):99-104.
10. Kuscu NK and Koyuncu F (2002): Hyperemesis gravidarum: current concepts and management. *Postgrad. Med. J.*, 78 (916):76-79.
11. Verberg MF, Gillott DJ, Al-Fardan N and Grudzinskas JG (2005): Hyperemesis

- gravidarum, a literature review. *Hum Reprod Update*, 11 (5):527-39.
12. Asakura H, Watanabe S, Sekiguchi A, Power GG and Araki T (2000): Severity of hyperemesis gravidarum correlates with serum levels of reverse T3. *Arch. Gynecol. Obstet.*, 264:57-62.
  13. Panesar NS, Li CY and Rogers M S (2001): Are thyroid hormones or hCG responsible for hyperemesis gravidarum? A matched paired study in pregnant Chinese women. *Acta Obstet. Gynecol. Scand.*, 80:519-524.
  14. Al-Yatama M, Diejomaoh M, Nandakumaran M, Monem RA, et al. (2002): Hormone profile of Kuwaiti women with hyperemesis gravidarum. *Arch. Gynecol. Obstet.*, 266: 218-222.
  15. Kennedy RL and Darne J (1991): The role of hCG in regulation of the thyroid gland in normal and abnormal pregnancy. *Obstet Gynecol*, 78:298-307.
  16. Jeffcoate WJ and Bain C (1985): Recurrent pregnancy-induced thyrotoxicosis presenting as hyperemesis gravidarum. *Br J Obstet Gynaecol* 92:413-415.
  17. Kimura M, Amino N, Tamaki H, Ito E, Mitsuda N, et al. (1993): Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. *Clin. Endocrinol. (Oxf)*, 38 (4): 345-350.
  18. Lao TT, Chin RK and Chang AM (1987): The outcome of hyperemetic pregnancies complicated by transient hyperthyroidism. *Aust NZ Obstet Gynaecol*, 27:99-101.
  19. Price A, Davies R, Heller SR, Milford-Ward A and Weetman AP (1996): Asian women are at increased risk of gestational thyrotoxicosis. *J Clin Endocrinol Metab*, 81:1160-1163.
  20. Zelkowitz P (1996): Childbearing and women's mental health. *Trans Psy Res*, 33:391-411.
  21. Klebanoff MA, Koslowe PA, Kaslow R and Rhoads GG (1985): Epidemiology of vomiting in early pregnancy. *Obstet Gynaecol*, 66:612-616.
  22. Leylek OA, Cetin A, Toyaksi M and Erselcan T (1996): Hyperthyroidism in hyperemesis gravidarum. *Int. J. Gynaecol. Obstet.*, 55 (1):33-37.
  23. Tareen AK, Baseer A, Jaffry HF and Shafiq M (1995): Thyroid hormone in hyperemesis gravidarum. *Asia-Oceania Journal of Obstetrics and Gynaecology, currently known as: J. Obstet. Gynaecol.*, 21 (5): 497-501.
  24. Chang JH, Kim GH, Kim HW, Jun HA, Lee KH, et al. (1997): Thyroid Hormone in Hyperemesis Gravidarum. *Korean J Obstet Gynecol.*, 40 (10):2153-2158.
  25. Tan EJ and Hershman JM (2009): Hyperthyroidism and Trophoblastic Disease. In: *Clinical Management of Thyroid Disease*, 1st ed., Saunders, ch. 16: 229-240.
  26. Nadungu JR, Amayo A, Qureshi ZP and Kigundu CS (2009): Gestational thyrotoxicosis associated with emesis in early pregnancy. *East Afr Med J.*, 86 (2): 55-8.
  27. Mestman JH (2007): Thyroid and Parathyroid Diseases in Pregnancy. In: *Gabbe: Obstetrics: Normal and Problem Pregnancies*, 5th ed, Churchill Livingstone, chapter 38: 1012- 1038.

8/15/2017