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ORIGINAL ARTICLE

Evaluation of Thyroid Funtion Tests in Patients with Hyperemesis Gravidarum

Najafipour F[a], Ghoddousi K[b], Zareizadeh M[b], Fardiazar Z[b]

[a]Department of Endocrinology and Metabolism, Sina Hospital and [b] Department of Obstetrics and Gynecology, Al-Zahra Hospital Tabriz University of Medical Sciences, Tabriz I.R. Iran

Hyperemesis gravidarum occurs in about 1.5% of pregnancies and is more common in Asian than in white women. Many patients do not need anti thyroid drugs, except for those with severe nausea and vomiting and thyroid dysfunction after 18-20 weeks of pregnancy. The aim of the study was to determine the importance of routine assessment of thyroid function in pregnant women with hyperemesis gravidarum, especially those with clinical features of hyperthyroidism.

Materials and Methods: 135 patients with hyperemesis gravidarum admitted to an Ob-Gyn hospital were selected. After excluding criteria, 103 patients underwent investigations including thyroid function tests and β-hCG.

Results: 35 women were found to have abnormal thyroid function tests with FT4I 4.74 ± 0.54 and in another group (68 women) this was 2.9±0.39 (P<0.0001). B-hCG in first group was 59406±14899 mIU/mL and in second group was 6750±3476 mIU/mL (P<0.0001). In 5 patients, PTU was started due to severe signs and symptoms of hyperthyroidism. Thyroid function tests were done for all of 35 patients after 4 weeks routine therapy for hyperemesis gravidarum. Thyroid function tests normalized in 11 patients with hyperemesis graridarum but remained abnormal in 22 patients hence; PTU was started and anti-TPO anti-body was measured; thyroid function tests were repeated monthly for all of them and PTU were adjusted accordingly. Means for duration and dose of therapy were 2.76 months and 60.63 mg/d for Anti-TPO negative and 5.33 months and 170 mg/d for Anti–TPO positive patients respectively.

Conclusion: In our study, thyroid, dysfunction in hyperemesis gravidarum was 35%, with 20% of the patients needing anti-thyroid therapy. A female predominance among offspring of mothers with hyperemesis gravidarum was observed. Routine assessment of thyroid function is necessary for women with hyperemesis gravidarum especially in patients with clinical features of hyperthyroidism. PTU needs to be considered in hyperemesis gravidarum with severe weight loss, vomiting and biochemical hyperthyroidism.

Correspondence: Farzad Najafipour, Department of Endocrinology and Metabolism, Sina Hospital, Tabriz University of Medical Sciences, Tabriz, I.R. Iran; *E-mail:* Najafipour @tbzmed.ac.ir

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Introduction

Human chorionic gonadotropin is composed of α-and β-subunits. The α-subunit is identical to the α-subunit of TSH, luteinizing hormone, and follicle-stimulating hormone. The β-subunit of hCG has considerable structural homology with the β-subunit of TSH, but it is larger because it contains a 21-amino-acid carboxy-terminal tail.

Hyperemesis gravidarum is marked by profound vomiting during early gestation, which may result in electrolyte imbalance and dehydration. High serum free T4 and T3 concentrations are a common finding in women with hyperemesis gravidarum, having been reported in 25% to 75% of patients in various series.[1] Women with hyperemesis and high serum free T4 and T3 concentrations have higher serum hCG concentrations than normal pregnant women.[1] Their serum hCG concentrations correlate with the degree of elevation of serum free T4 and T3 concentrations and with serum thyroid-stimulating activity, as measured by bioassay. Vomiting is also more severe in women who have higher serum hCG concentrations, suggesting that another factor induced by hCG, perhaps estradiol, may be responsible for the vomiting.[2] Women with twin pregnancies have higher serum hCG concentrations than do women with singleton pregnancies, and are more likely to have hyperemesis gravidarum.[3] There is confusion about the extent that hyperemesis gravidarum is associated with thyrotoxicosis.[2] The hyperthyroxinemia is usually transient, resolving by 18 weeks gestation without antithyroid therapy.[3] There is debate about hyperthyroxinemia during the common "morning sickness" of pregnancy; these patients demonstrate few overt manifestations of thyrotoxicosis. The best evidence supporting the hypothesis that hCG is the cause of the thyroid stimulation in hyperemesis gravidarum and is closely linked to the cause of the hyperemesis.[4] The degree of thyroid stimulation varies with the hCG concentration and correlates with the symptoms of hyperemesis.[3,5] Antithyroid therapy should be considered for women with persistent hyperemesis and hyperthyroxinemia past 20 weeks gestation.[6]

Materials and methods

One hundred and thirty-five women were admitted with hyperemesis gravidarum, of which 32 patients were excluded due to other illnesses such as diabetes mellitus and thyroid disease or those with a history of specific drugs such as antithyroid drugs or levothyroxine. Each woman was examined for clinical signs of thyroid disease and underwent investigations including electrolytes, liver enzyme test, β-hCG, urine ketone, and thyroid function tests (TFT) as well.

The severity of the hyperemesis gravidarum was evaluated by the degree of ketonuria and weight loss. An ultrasound to confirm the gestational age and multiple gestation and to exclude a trophoblastic disease was carried out. In patients with abnormal thyroid function test (biochemical hyperthyroidism), anti–TPO was measured. In patients with severe signs and symptoms of hyperthyroidism, PTU was started, and if not, TFTs were repeated 4 weeks later. SPSS software version 11 was used for statistical analysis and t-test was performed for comparisons between groups.

All data are presented as mean±SE and values of $p<0.05$ were considered statistically significant.

Table 1. Characteristics of parameters in 103 patients

Parameters	Max	Min	Mean+SD
T4 (μg/dL)	20	9	13.13±2.4
T3 (ng/dL)	300	100	179.7±52.48
TSH (mU/L)	1	0.01	0.23±0.25
T3RU (%)	38	22	26.5±2.9
FT_4I	7.6	2/2	3.53±0.98
β-hCG (mIu/mL)	91200	1000	24643±26646
Na (meq/L)	146	128	133.89±3.45
K (meq/L)	3.9	2/9	3.31±0.27
ALT (U/L)	85	10	41.62±15.51
AST (U/L)	89	15	33.6±14.01
Weight loss (Kg)	8.9	3	4.88±1.1
Scores of nausea and vomiting	12	7	9.19±1.26

Results

Diagnosis and therapeutic algorithm of 135 patients with hyperemesis gravidarum are shown in Fig.1.

Table 1 represents the baseline characteristics of 103 patients with hyperemesis gravidarum. Mean age of pregnancy at the admission was 15.34 ± 2.61 weeks and age of starting vomiting was 7.42±2.14 weeks of gestation. Twenty-eight patients (27%) had a positive family history of hyperemisis gravidarum in first degree relative families. Forty-patients had gravida 2 or more and 25 (62.5%) of them had history of hyperemesis gravidarum in a previous pregnancy. Thirty-five patients (34%) had biochemical hyperthyrodism (suppressed thyroid stimulating hormone and increased free tetraiodothyronine index), and 68 patients (66%) had normal thyroid tests. Characteristics of the two groups are compared in Table 2.

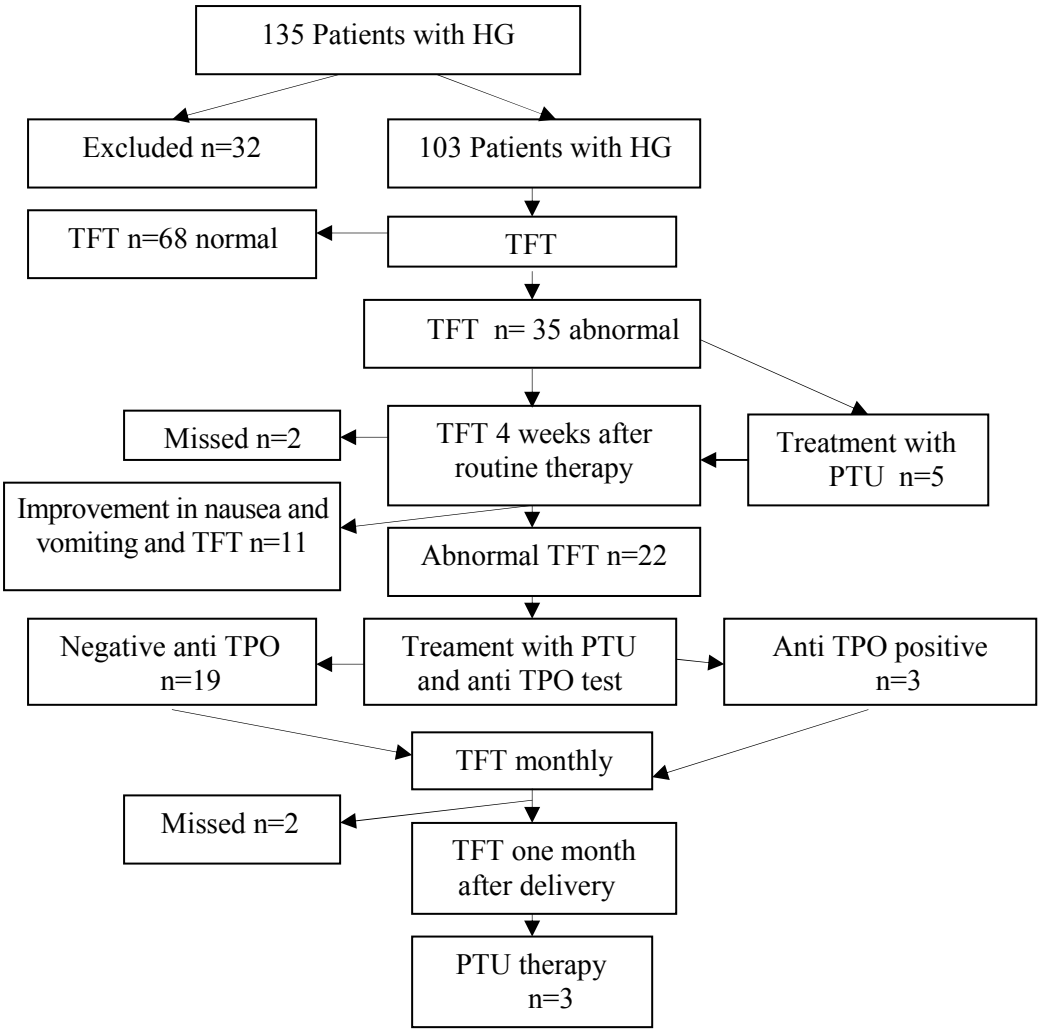

Fig.1. Algorithm of diagnosis and treatment in patients

Table 2. Comparison of parameters in the two groups

Parameters	Normal TFT N=68	Abnormal TFT N=35	P-Value
Age (years)	23.73±3.85	23.74±4.27	NS
β-hCG (mIu/mL)	3476 ± 6750	59406±14899	<0.0001
FT_4I	2.9±0.39	4.74±0.54	<0.0001
TSH (mU/L)	0.21±0.14	0.08±0.05	<0.0001
T_3 (ng/dL)	148.55±30.3	240±27.4	<0.0001
T4 (µg/dL)	11.67±1.38	15.97±0.99	<0.0001
T_3RU (%)	24.84±1.65	29.65±2.12	<0.0001
Na (meq/L)	134.5±3.74	132.68±2.4	<0.01
K (meq/L)	3.36±0.27	3.2±0.22	<0.03
ALT (U/L)	26.82±8.16	46.77±17.9	<0.0001
AST (U/L)	36.54±10.73	51.48±14.69	<0.0001
Weight loss (kg)	4.91±1.5	4/82±1/2	NS
Nausea and vomiting (w2)	7.3±3.2	7.62±2.04	NS
Gestational age (w2)	15.36±2.8	15.31±2.24	NS
Score of nausea and vomiting	8.67±0.98	10.2±1.15	<0.0001
Orthostatic hypotension (PR3)	54 (37%)	34 (97%)	<0.0001
Orthostatic hypotension (BP4)	60(41%)	%) 91(32	<0.0001
Degree of goiter (2&3)	7 (5%)	%) 71 (25	<0.0001

NS = Non significance; W = Week; PR = Pulse rate; BP = Blood pressure; * Mean±SD.

PTU was started in 5 patients at time of diagnosis due to severe biochemical and clinical signs and symptoms of hyperthyroidism. Mean dose of PTU was 170±55 mg/d. Thyroid function tests were repeated after one month; they had normalized in 11 patients (31.42%) and 2 patients were missed while 22 patients (68.85%) still had abnormal TFTs. PTU was started for them with a mean dosage of 60 mg/d and TFTs were repeated monthly (Fig.1). Stages of goiter in the two groups are shown in Fig.2.

Anti TPO measurements in 22 patients were negative whereas in 3 of them these were positive with mean ± SD 145±73.1 IU/mL.

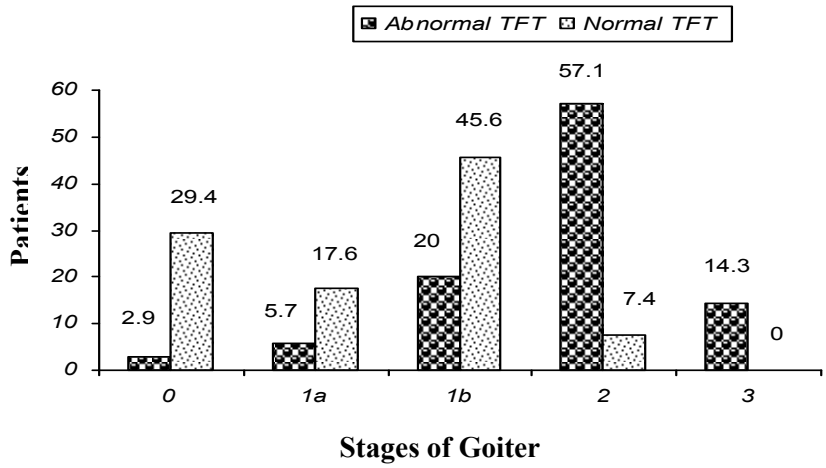

Fig.2. Comparison of goiter in the two groups

Discussion

Hyperemesis gravidarum is characterized by nausea and vomiting, which in severe cases may lead to dehydration and require hospitalization.[4] Elevated serum T4 and decreased serum TSH concentrations may be found in as many as half or more of pregnant women with hyperemesis gravidarum. Mild hyperthyroidism may be associated with hyperemesis gravidarum, perhaps due to higher serum concentrations of human chorionic gonadotropin which may have more thyroid stimulating activity.[7] The thyroid-stimulating activity of hCG has been elucidated by a variety of studies. Human chorionic gonadotropin inhibits the binding of labeled TSH to its plasma membrane receptors on thyroid follicular cells, and activates adenylyl cyclase in rat thyroid cells and cells transfected with human TSH receptors.[7] Human chorionic gonadotropin increases iodide uptake by increasing the expression of the sodium/iodide transporter on thyroid cells.[8]

The thyroid-stimulating activity of hCG has been demonstrated in mice, rats, chicks, and humans. Injection of large amounts of hCG (100,000 to 150,000 U) into normal men stimulates thyroid iodine release.[7] In normal pregnant women, serum TSH concentrations decrease from 9 to 12 weeks of gestation when serum hCG concentrations are highest, while 3% of pregnant women have transient subclinical thyrotoxicosis (low serum TSH and normal serum free T4 and free T3 concentrations) at that time. The high serum hCG concentrations correlated with increased thyroid-stimulating activity in a mouse bioassay.[8] One report found low serum TSH concentration more often in women with hyperemesis gravidarum than in normal pregnant women (60% versus 9%). Some of these women had elevated serum free T4 concentrations and therefore had hyperthyroidism.[8] In several studies, thyroid dysfunction is reported to range from 25% to 75%.[6] In our study thyroid dysfunction was 34% in subjects with hyperemesis gravidarum. Most of the patients had over 5% weight loss (4.88±1.1 kg) especially those with thyroid dysfunction (Table 2). Scores of nausea and vomiting with Rhodes index[9] criteria were higher in patients with thyroid dysfunction ($p<0.0001$). Hyperthyroid patients were more likely than euthyroid patients to have abnormal electrolyte levels or increased liver enzymes (Table 2).

This finding also shows that the varying severity of hyperemsis and weight loss were found to be directly associated with the degree of hyperthyroidism. The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some have argued that hyperthyroidism is the cause of the hyperemesis, whereas others have argued to the contrary.[8] The recent report by Rodien et al. describing two patients with hyperemesis and hyperthyroidism attributable to hCG–hypersensitive thyrotropin receptors, suggests that hyperemesis can be directly related to the overactive thyroid and not necessarily to the effects of excess hCG.[10]

It has been shown that hyperthyroidism is associated more with trophoblastic tumor than with hyperemesis gravidarum.[11] In trophoblastic disease, the spectrum of alterations of thyroid function ranges from a small increase in serum free T4 and T3 concentrations, as evidenced by a low basal serum TSH concentration or a subnormal serum TSH response to TRH,[12] to moderate increases in serum free T4 and T3 concentrations with no symptoms of thyrotoxicosis, and to marked increases with severe clinical thyrotoxicosis or even thyroid storm[4]. The lack of clear clinical features of thyrotoxicosis in many patients with high serum free T4 and T3 concentrations may be attributable to the relatively brief duration of the increased thyroid function, so that there is insufficient time to develop overt clinical thyrotoxicosis.[7] The etiology of the hyperthyroidism is thought to be related to the increased concentrations of serum hCG in these patients, which can be 1000 fold higher than reference

values. As mentioned previously, prolonged increase in serum hCG can clearly cause a significant increase in thyroid function. Complete surgical removal of the trophoblastic tumor rapidly cures the hyperthyroidism.[11]

In our study, β-hCG was significantly higher in hyperthyroid patients than in patients with normal thyroid function and TSH was significantly suppressed in the first group.

Twin or more gestations are more often associated with sustained elevation of β-hCG and 60% suppression of TSH and hyperemesis gravidarum are more frequent in these groups than in the single fetus.[12] In this study, stage of goiter was more advanced in hyperthyroid patients than in patients with normal thyroid function. The prevalence of goiter during pregnancy varies with geographic locations. In a study done in Scotland in which iodine intake was marginal, 70% of pregnant women were diagnosed as having goiter, in contrast to 38% of non-pregnant women.[13] The same investigator repeated the study in Iceland where the diet is iodine-rich and no significant increase in goiter was noted during pregnancy (19% versus 23% respectively).[13] In our study, stage 2 and 3 goiters diagnosed with WHO criteria, were detected in 75% of hyperemesis gravidarum with thyroid dysfunction and stage 2 goiter in 7.5% in the second group (Fig.2). The results of the present research also show that advanced stages of goiter are more common in hyperemesis gravidarum with thyroid dysfunction, results not reported in other studies.

Women with twin pregnancies have higher serum hCG concentrations than do women with singleton pregnancies, and are more likely to have hyperemesis gravidarum.[14] Our results are suggestive of the involvement of hyperthyrodism and fetal sex in the pathegenesis of hyperemesis gravidarum, findings observed in several studies.[15] We reported a female predominance among the offspring of mothers with hyperemesis grariarum. In this study,[14] female and 9 male infants were delivered and 16 uni fetus, 2 twins and one triple fetus were noted.

Although clinical features of thyrotoxicosis women with hyperemesis gravidarum are usually absent, or overlooked, some have clinically evident thyrotoxicosis.[16,12] The thyrotoxicosis of hyperemesis gravidarum usually resolves spontaneously within several weeks as the vomiting disappears.[17,18] But in some of them, it is associated with the most severely thyrotoxic cases, and the symptoms may become sufficiently alarming enough to require hospitalization for treatment. In these relatively rare instances, the severity of clinical presentation may require treatment with PTU, usually administered for only a few weeks, because free T4 normalizes simultaneously with the decrease in hCG concentrations.[14] In our study, hyperthyroidism was severe in five patients and PTU was started following diagnosis. Three of them were anti-TPO antibody positive. In other patients TFTs were repeated 4 weeks later (Fig.1). In patients with anti-TPO antibody positive, PTU was started with a mean dose of 170±57 mg/d for 5.33±0.5 months during pregnancy and continued for one month after delivery. Serial TFTs were done monthly. FT_4I and TSH in hyperthyroid patients with anti-TPO negative were 4.73±0.3 and 0.11±0.08 mu/mL respectively in this group. PTU was started during pregnancy with a mean dose of 60 mg/d and duration of 2.67±2.16 months.
In this study, PTU therapy significantly improved hypermesis within several weeks. Improvement of nausea, vomiting and significant weight gain (1.25±0.38 kg/month) were noted.

Pregnant women tolerate mild to moderate degrees of hyperthyroidism relatively well. If the diagnosis is doubtful, thyroid function tests can be repeated in 3 or 4 weeks before making a final decision.[6,12] Determination of anti-TPO may be helpful in alerting the physician to the possibility of Graves' disease.

Finally routine assessment of thyroid function is necessary for women with hyperemesis gravidarum especially in patients with

clinical features of hyperthyroidism. Symptoms of hyperemesis gravidarum usually resolve by 18th week of gestation, regardless of therapy. Antithyroid therapy should be considered for women with persistent hyperemesis and hyperthyroxinemia past the 18-20th week of gestation, especially in patients with hyperemesis gravidarum and severe weight loss, vomiting and biochemical hyperthyroidism.[6,12,14]

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