Erciyes Med J 2015; 37(4): 128-32 • DOI: 10.5152/etd.2015.6577

Investigating Maternal Serum Thyroid Hormone, Beta-Human Chorionic Gonadotropin (Beta-HCG) and Free Beta-HCG Levels in Hyperemesis Gravidarum

ORIGINAL INVESTIGATION

Uğur Atmaca[1], Mehmet Aral Atalay[2], Necati Özçimen[3], Bilhan Sidal[4], Uğur Ateş[4]

ABSTRACT

Objective: To investigate the influence of thyroid hormones, beta human chorionic gonadotropin (β-HCG), and free β-HCG (fβ-HCG) in the etiology of hyperemesis gravidarum (HG) and to determine the main hormone that is responsible for the exacerbation of symptoms.

Materials and Methods: Serum thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), β-HCG, and fβ-HCG levels were measured twice (before and after hospitalization) in 55 patients with HG and measured once in 64 healthy controls. Serum hormone levels were determined using enzyme-linked immunosorbent assay.

Results: Decreased mean TSH and increased mean fT4 levels were found in the pre-treatment serum samples of the HG group compared with the control group. Both differences were statistically significant (p=0.020 and p=0.007, respectively). However, there was no statistically significant difference in mean fT3, β-HCG, and fβ-HCG levels between the pre-treatment serum samples of the HG group and control group. We could not demonstrate any correlation between the levels of β-HCG and thyroid hormones in the HG group; however, fβ-HCG moderately correlated with fT4 levels (r=0.494).

Conclusion: The presence of hyperthyroidism was observed as the leading alteration in HG. In this study, fβ-HCG was demonstrated to have no direct effect on the etiology of HG; however, a possible indirect effect of fβ-HCG in relation with thyroid hormones was indicated. Hyperthyroidism was assessed to be primarily responsible for the symptoms in HG.

Keywords: Hyperemesis gravidarum, thyroid hormones, TSH, β-HCG, free β-HCG

[1]Clinic of Gynecology and Obstetrics, Private Sandeva Gynecology and Obstetrics Center, Afyon, Turkey

[2]Department of Gynecology and Obstetrics, Uludağ University Faculty of Medicine, Bursa, Turkey

[3]Clinic of Gynecology and Obstetrics, Konya Dr. Faruk Sükan Maternity and Child Hospital, Konya, Turkey

[4]Clinic of Gynecology and Obstetrics, Bezmialem Valide Sultan Vakıf Gureba Eğitim Training Hospital,İstanbul, Turkey

Submitted
15.11.2013

Accepted
04.01.2014

Correspondance
Dr. Mehmet Aral Atalay, Uludağ Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Bursa, Türkiye
Phone: +90 539 376 00 24
e.mail: maralatalay@gmail.com

INTRODUCTION

Almost half of all pregnant women experience nausea and vomiting known as "morning sickness" in the first trimester of pregnancy (1, 2). The condition generally starts between the 6th and 8th week and subsides at the end of the first trimester or early in the second trimester (2, 3). Although the vast majority of pregnant women adapt to the situation, in 10% of cases, nausea and vomiting can be severe, resulting in nutritional problems (3). Additional symptoms may include weight loss, dehydration, electrolyte imbalance, hypochloremic alkalosis, and ketonuria. This clinical situation, known as hyperemesis gravidarum (HG), if not treated, can lead to hepatorenal disorders, locomotor system disorders, peripheral neuropathies, and degenerative encephalopathies (4-8). This clinical status has been reported in 0.3–0.5% of all live births (1, 2). The etiology of HG is unknown; however, hormonal, metabolic, neurotic, and psychosomatic disorders are thought to be the etiological factors (9-11).

In response to the metabolic needs of pregnancy, the basal metabolism increases and the thyroid gland enlarges, resulting in increased hormone secretion (12-14). Increased thyroid activity during pregnancy is compensated by a significant increase in the levels of circulating thyroxine-binding globulin (TBG) in response to high levels of estrogen. As a result, a new equilibrium is established as the amount of the bound thyroid hormone is increased, resulting in pregnant women to become euthyroid (Figure 1) (12-14). However, patients diagnosed with HG have been shown to have a temporary clinical status of significant biochemical hyperthyroidism compared with the controls (15-18). Non-specific symptoms seen in HG, such as tachycardia, nausea, vomiting, and fatigue, are in all likelihood due to hyperthyroidism.

Thyrotropic substances secreted by the placenta, such as chorionic thyrotropin and human chorionic gonadotropin (HCG), were also investigated for the increase in thyroid activity (2). As a consequence, studies reporting elevated levels of beta HCG (β-HCG) in patients with HG were published (19-22).

In general, unbound free fragments of hormones are expected to have both biological and physiological effects. Therefore, increased free β-HCG (fβ-HCG) levels may be important in the emergence and course of HG (23). To date, there have been very few studies investigating the relationship between β-HCG, fβ-HCG, other hormones,

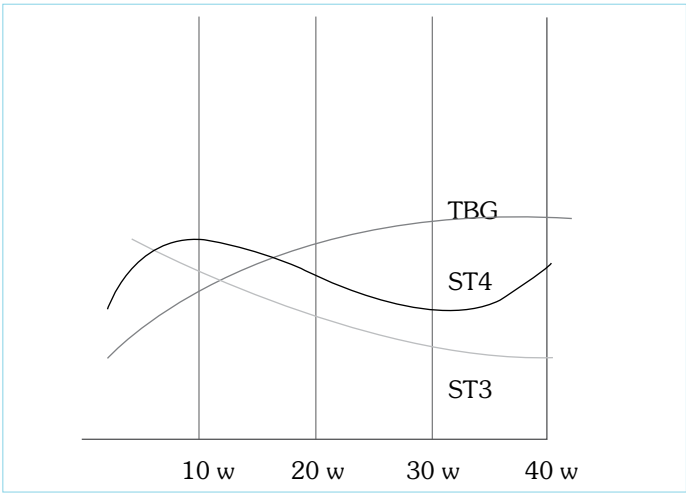

Figure 1. Compensation of thyrotrophic activity by increased TBG levels throughout pregnancy (Note the increase in TBG levels in the first and early second trimester)
TBG: thyroxine-binding globulin; ST3: free triiodothyronine; ST4: free thyroxine

and serum macromolecules in patients with HG (24, 25). Consequently, we investigated the effects of the thyroid hormones, β-HCG, and fβ-HCG and their possible interactions with each other in the etiology of HG.

MATERIALS and METHODS

This study was based on the analyses of 55 women with first-trimester singleton pregnancies, all of whom were hospitalized after being diagnosed with HG between May 2008 and December 2011. The control group consisted of 64 healthy pregnant women, who were referred to our outpatient clinic without any complaints during the same period. The criteria for the diagnosis of HG were vomiting more than three times a day, weight loss of more than 5% of body weight compared with that at the onset of pregnancy, and ketonuria of +3 in at least two randomly collected urine samples. Patients with a history of liver, gastrointestinal tract, or thyroid disease (overt hypothyroidism, nodular hyperthyroidism, Graves' disease, Hashimoto's thyroiditis) or findings in the abdominal ultrasonography, thyroid ultrasonography, and liver function tests suggesting these diseases were excluded. Patients with other conditions or psychosomatic disorders that may cause nausea and vomiting were also excluded from the study. A detailed medical history was obtained, and a physical examination was performed in all cases. Gestational ages of the participants were determined from the last menstrual period. Gestational age was determined with transvaginal ultrasonography for the participants who did not know the exact date of their last menstrual period. The study was conducted after obtaining the required ethics approval and a written informed consent from all participants.

Peripheral venous blood samples were obtained from the patients to determine the serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), and fβ-HCG levels. The first sample was obtained on the day of admission. The second was obtained on the day after the discontinuation of vomiting and when nausea was experienced less than three times a day and ketonuria could not be detected. At each time, 3 mL of peripheral venous blood was collected from the participant in the morning on an empty stomach. Samples were obtained from the gestational age-matched healthy pregnant control group once in the morning on an empty stomach. Following admission, the patients were treated with intravenous fluid replacement. Oral food intake was restricted. Antiemetics (5 mg metoclopramide ampule, three times a day), antihistaminics (25 mg meclizine tablet, two times a day), and vitamin B6, to prevent Wernicke's encephalopathy, were added to the therapy. When the complaints of nausea and vomiting subsided, the oral intake of small amounts of food was restarted at frequent intervals, alongside the intravenous fluid replacement therapy. The patients whose incidences of vomiting and nausea reduced to less than three times a day and who were negative for ketonuria were discharged.

For the measurements of serum fT3 and fT4 levels, an Immulite® 2000 xpi Immunoassay System (Siemens AG, Erlangen, Germany) device was used, along with a separate enzyme-linked immunosorbent assay (ELISA) kit for each analysis. The measurement of serum TSH levels was performed with an Immulite® 2000 third generation TSH ELISA kit. In total, 1.8–4.2 pg/mL, 0.8–1.9 ng/dL, and 0.4–4 mIU/mL values were taken as reference values for fT3, fT4, and TSH, respectively. For the measurement of β-HCG levels, a GWB-519AAA (Genway Biotech, San Diego, CA) ELISA kit was used. A GWB-59616E (Genway Biotech, San Diego, CA) ELISA kit was used for the measurement of fβ-HCG levels.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 17.0 (SPSS Inc.; Chicago, IL, US). For the comparison of the continuous variables between the two groups, depending on the distribution of the sample group, Student's t-test or Mann–Whitney U test was performed, as appropriate. The chi-square test was used for the comparison of categorical variables. Because the fT3, fT4, TSH, β-HCG, and sβ-HCG levels were not distributed normally, correlation analyses with the Spearman's rank correlation coefficient were considered. Because gestational age, age, and body mass index were considered to have a possible unexpected effect as confounding variables, analysis of covariance was performed to compare the data. A p value of <0.05 was considered as statistically significant.

RESULTS

In the HG group, the patients' age ranged between 18 and 36 years (mean: 26.54±4.64 years). The age of the patients in the control group was between 19 and 37 years (mean: 28.18±4.88 years). The demographic characteristics of the HG and control groups are shown in Table 1. There were no statistically significant differences between the groups in terms of age, weight, height, BMI, gravidity, parity, abortion, or gestational age.

In the HG group, 37 of the 55 patients (67.3%) had low levels of TSH, 21 (38.2%) had high levels of fT3, and 16 (29.1%) had high levels of fT4 compared with the reference values. The mean duration of hospitalization was found to be 6.96±1.04 days in the HG group.

Pre-treatment TSH, fT3, and fT4 values of the HG group were compared with those of the control group (Table 2). TSH levels in the HG group were found to be significantly lower, whereas fT4 lev-

Table 1. Demographic characteristics of the study population

	HG group (n=55)	Control group (n=64)	Significance
Age (years)	26.54±4.64	28.18±4.88	0.183
Weight (kg)	56.79±10.25	61.59±11.60	0.093
Height (cm)	157.68±6.57	158.91±7.28	0.490
BMI (kg/m^2)	22.76±3.31	24.34±4.06	0.102
Gravidity	2.79±1.55	2.85±1.42	0.857
Parity	1.21±1.07	1.32±1.09	0.757
Number of abortions	0.32±0.67	0.50±0.75	0.215
Gestational age (weeks)	9.18±1.93	6.96±1.04	0.403

Values are given as mean ± SD
BMI: body mass index; SD: standard deviation

Table 2. Differences between pre-treatment values of HG and control groups

	HG group	Control group	Significance
TSH	0.55±0.88	1.03±0.68	0.020
fT3	4.41±1.31	3.84±0.60	0.064
fT4	1.72±0.53	1.38±0.20	0.007
β-HCG	7900±17626	76079±24899	0.063
fβ-HCG	114.14±60.36	116.56±76.5	0.892

Values are given as mean ± standard deviation SD
fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid-stimulating hormone; β-HCG: beta human chorionic gonadotropin; fβ-HCG: free beta human chorionic gonadotropin; HG: hyperemesis gravidarum; SD: standard deviation

els were significantly higher than the control group (p=0.020 and p=0.007, respectively). The difference between the two groups in terms of mean fT3 levels did not reach statistical significance (p=0.064). In the HG group, the difference in mean fT4 levels between pre- and post-treatment values was statistically significant (p=0.019); however, the differences in mean TSH and fT3 levels were not statistically significant (Table 3). There was no statistically significant difference between the post-treatment values of the HG group and control group in terms of TSH, fT3, and fT4 levels (Table 4).

In addition, there was no statistically significant difference between the groups in terms of mean fβ-HCG levels. Although higher fβ-HCG values were obtained in HG patients than in the control group, the difference in mean fβ-HCG levels between both groups did not reach statistical significance. We could not demonstrate a strong correlation between β-HCG and TSH, fT3, and fT4 levels in patients with HG. However, there was a weak inverse correlation between fβ-HCG and TSH levels, a weak correlation between fβ-HCG and fT3 levels, and a moderate correlation between fβ-HCG and fT4 levels in the HG group (r=−0.255, r=0.305, and r=0.494, respectively).

Table 3. Differences between pre- and post-treatment values in HG group

	Pre-treatment values	Post-treatment values	Significance
TSH	0.55±0.88	0.62±1.02	0.144
fT3	4.41±1.31	3.95±1.26	0.065
fT4	1.72±0.53	1.56±0.59	0.019
β-HCG	87900±17626	94588±10249	0.034
fβ-HCG	114.14±60.36	119.40±65.38	0.366

Values are given as mean ± SD
fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid-stimulating hormone; β-HCG: beta human chorionic gonadotropin; fβ-HCG: free beta human chorionic gonadotropin; HG: hyperemesis gravidarum; SD: standard deviation

Table 4. Differences between post-treatment values of HG and control groups

	HG group	Control group	Significance
TSH	0.62±1.02	1.03±0.68	0.068
fT3	3.95±1.26	3.84±0.60	0.420
fT4	1.56±0.59	1.38±0.20	0.671
β-HCG	94588±10249	76079±24899	0.002
fβ-HCG	119.40±65.38	116.56±76.50	0.877

Values are given as mean ± SD
fT3: free triiodothyronine; fT4: free thyroxine; TSH: thyroid-stimulating hormone; β-HCG: beta human chorionic gonadotropin; fβ-HCG: free beta human chorionic gonadotropin; HG: hyperemesis gravidarum; SD: standard deviation

DISCUSSION

Because the etiology of HG is uncertain and the mechanisms that initiate the disease are not well known, endocrine and metabolic disorders have been the subject of much research (9-11). The theory put forward here was that patients with HG have elevated β-HCG and fβ-HCG levels, which stimulate the thyroid gland because of their similarity with Thyrotropin-releasing hormone and induce a temporary clinical or biochemical hyperthyroidism.

Bouillon et al. (26) observed high fT4 levels in 25 (73%) of 33 cases with HG, with high fT3 levels in 11 (33%) of these, and they reported that there was no TSH response after TRH injection. In that study, it was observed that hyperthyroxinemia was cured in patients with HG within a few weeks after conservative treatment, and it did not relapse in the latter weeks of pregnancy. Similarly, in a study with 71 participants, Swaminathan et al. (27) found elevated levels of fT4 in 1 of 3 and fT3 in 1 of 5 of the patients with HG. They also reported high levels of HCG in the group that displayed high levels of thyroid hormones.

In this study, although non-specific symptoms of hyperthyroidism (such as vomiting and weight loss) were observed, no significant clinical evidence of thyrotoxicosis was encountered. Two patients

who were admitted after being diagnosed with HG had significant goiters and because these two patients also had positive laboratory findings of hyperthyroidism, they were excluded from the study. In HG group, an increase in fT4 and fT3 levels and a decrease in TSH levels were determined before treatment, which was consistent with the findings of previous studies (15, 16, 18, 19, 27). In addition, in the HG group, when pre- and post-treatment values were compared, the main difference observed was in fT4 levels. fT4 levels were increased in the pre-treatment samples, causing a drop in TSH levels. Because conservative therapy improved TSH suppression, fT4 levels decreased to normal values. In other words, a clinical status of temporary biochemical hyperthyroidism has been observed in patients, although they became euthyroid after a conservative treatment. These findings are consistent with those of previous studies (15, 16, 18). In patients with HG, the low rate of increase in fT3 may be due to the fact that the disease is an acute pathology. In cases of acute illness and malnourishment, the peripheral conversion of T4 to T3 is decreased (28-30). In our study, the increase in fT4 was found to be more prominent. Furthermore, the lack of significant symptoms of hyperthyroidism in patients with HG may be due to relatively low levels of fT3; additionally, in cases of hunger, it may be due to a reduction in the concentration of thyroid hormone receptors (2).

Goodwin et al. (31) found higher levels of β-HCG in patients with biochemical hyperthyroidism, and they reported that β-HCG levels were correlated with the severity of vomiting. In a similar study, Leylek et al. (32) have shown that fT3, fT4, and β-HCG levels are significantly higher in patients with HG than in the control group. Hershman et al. (33) have demonstrated that β-HCG increases the transport of cyclic adenosine monophosphate and iodine, and it also accelerates cell growth in the Fischer rat thyroid cell line (FRTL-5). The authors have shown that changes in the molecular structure of β-HCG resulted in different degrees of stimulation of the TSH receptors. However, our study revealed that although the β-HCG levels were higher in patients with HG than in the control group, the difference was not statistically significant. In addition, no statistically significant difference was found between mean fβ-HCG levels of both groups. On the other hand, in the HG group, there was a statistically significant difference between the pre- and post-treatment values of β-HCG, which are thought to be increased because of the progress in pregnancy, but independent of the current clinical situation. With respect to the correlation analysis of the pre-treatment values in the HG group, a weak inverse correlation was identified between fβ-HCG and TSH levels, a weak correlation was noted between fβ-HCG and fT3 levels, and a moderate correlation was demonstrated between fβ-HCG and fT4 levels. The lack of a statistically significant difference in fβ-HCG levels between the groups prevents us from concluding that fβ-HCG had a direct effect on the increase of fT4; additionally, there was no correlation between β-HCG and TSH and fT3 and fT4 levels, which contradicts the findings presented in previous literature (15, 16, 18). fβ-HCG has also been reported to have no direct effect on the hypothalamus and pituitary gland.

One limitation of this study is the lack of measurements of TBG and sex hormone-binding globulin levels; however, the homogenized study group is well investigated from an etiological point of view, which is a strong aspect of this study.

CONCLUSION

In conclusion, a clinical picture of biochemical hyperthyroidism was observed in the HG group before treatment, and there were no significant differences between the groups in terms of thyroid hormones post-treatment. However, a rapid recovery of biochemical hyperthyroidism was observed in patients with HG after only symptomatic treatment. Hyperthyroidism was determined to be the primary cause of the symptoms of HG. In this study, it was concluded that there was no evidence of β-HCG in the etiology of HG, and fβ-HCG was found to have no direct effect on the etiology or symptoms, although it had an indirect effect through the thyroid hormones.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authors' Contributions: Conceived and designed the experiments or case: UA, MAA, BS, UA. Performed the experiments or case: UA, MAA, NÖ, BS, UA. Analyzed the data: UA, MAA, NÖ, BS, UA. Wrote the paper: UA, MAA, NÖ, BS. All authors read and approved the final manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Abell TL, Riely CA. Hyperemesis Gravidarum. Gastroenterol Clin North Am 1992; 21(4): 835-49.
2. Goodwin TM. Hyperemesis Gravidarum. Clin Obstet Gynecol 1998; 41(3): 597-605. [CrossRef]
3. Quinla JD, Hill DA. Nausea and vomiting of pregnancy. Am Fam Physician 2003; 68(1): 121-8.
4. Macle L, Varlet MN, Cathébras P. Hyperemesis gravidarum: a rare but potentially severe complication of the first trimester of pregnancy. Rev Prat 2010; 60(6): 759-64.
5. Massou S, El Fazazi H, Atmani M, Azendour H, Belyamani L, Kamili ND. Hypokaliemic myopathy: a rare complication of hyperemesis gravidarum. Ann Fr Anesth Reanim. 2009; 28(7-8): 713. [CrossRef]
6. Harish K, Nitha R, Harikumar R, Sunil Kumar K, Varghese T, Sreedevi NS, et al. Prospective evaluation of abnormal liver function tests in pregnancy. Trop Gastroenterol 2005; 26(4): 188-93.
7. Hill JB, Yost NP, Wendel GD Jr. Acute renal failure in association with severe hyperemesis gravidarum. Obstet Gynecol 2002; 100(5): 1119-21. [CrossRef]
8. Shalchian S, de Noordhout AM, Fumal A, Tebache M. A rare complication of hyperemesis during pregnancy: Wernicke's encephalopathy. Acta Neurol Belg 2010; 110(2): 209-11.
9. David M, Borde T, Siedentopf F. Do immigration and acculturation have an impact on hyperemesis gravidarum? Results of a study in Berlin/Germany. J Psychosom Obstet Gynaecol 2012; 33(2): 78-84. [CrossRef]
10. D'Orazio LM, Meyerowitz BE, Korst LM, Romero R, Goodwin TM. Evidence against a link between hyperemesis gravidarum and personality characteristics from an ethnically diverse sample of pregnant women: a pilot study. J Womens Health (Larchmt) 2011; 20(1): 137-44. [CrossRef]

11. Lewandowski K, Hincz P, Grzesiak M, Cajdler-Łuba A, Salata I, Wilczyński J, et al. New onset Addison's disease presenting as prolonged hyperemesis in early pregnancy. Ginekol Pol 2010; 81(7): 537-40.
12. Gilstrap LC. Maternal physiology. In Gary Cunningham FG, Hauth JC, Editors. Williams Obstetrics. 22nd ed. New York: McGraw-Hill Medical Publishing; 2005. p. 72-89.
13. Leung AM. Thyroid function in pregnancy. J Trace Elem Med Biol 2012; 26(2-3): 137-40. [CrossRef]
14. Lazarus JH. Thyroid function in pregnancy. Br Med Bull 2011; 97(1): 137-48. [CrossRef]
15. Goodwin TM, Montoro M, Mestman JH. Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol 1992; 167(3): 648-52. [CrossRef]
16. Gherman RB, Mestman JH, Satin AJ, Goodwin TM. Intractable hyperemesis gravidarum, transient hyperthyroidism and intrauterine growth restriction associated with hyperreactio luteinalis. A case report. J Reprod Med 2003; 48(7): 553-6.
17. Weng MT, Wei SC, Wong JM, Chang TC. Hyperemesis gravidarum presenting as jaundice and transient hyperthyroidism complicated with acute pancreatitis. J Formos Med Assoc 2005; 104(3): 194-7.
18. Albaar MT, Adam JM. Gestational transient thyrotoxicosis. Acta Med Indones 2009; 41(2): 99-104.
19. Yiğit MS, Erdoğan E, Cengiz C, Küçükömürcü Ş. Hiperemezis gravidarum olgularında tiroid fonksiyon değişiklikleri ve B-HCG düzeyleri. Jinekol Obstet Derg 1991; 5(2): 32-4.
20. Rodien P, Jordan N, Lefèvre A, Royer J, Vasseur C, Savagner F, et al. Abnormal stimulation of the thyrotrophin receptor during gestation. Hum Reprod Update. 2004; 10(2): 95-105. [CrossRef]
21. Hershman JM. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. Best Pract Res Clin Endocrinol Metab. 2004; 18(2): 249-65. [CrossRef]
22. Tan PC, Tan NC, Omar SZ. Effect of high levels of human chorionic gonadotropin and estradiol on the severity of hyperemesis gravidarum. Clin Chem Lab Med 2009; 47(2): 165-71. [CrossRef]
23. Cole LA. Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol 2010; 8(1): 102. [CrossRef]
24. Glinoer D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotrophin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest 1993; 16(11): 881-8. [CrossRef]
25. Goodwin TM, Hersman JM, Cole L. Increased concentration of the free beta-subunit of human chorionic gonadatropin in hyperemesis gravidarum. Acta Obstet Gynecol Scand 1994; 73(10): 770-2. [CrossRef]
26. Bouillon R, Naesens M, Van Assche FA, De Keyser L, De Moor P, Renaer M, et al. Thyroid function in patients with hyperemesis gravidarum. Am J Obstet Gynecol 1982; 143(8): 922-6.
27. Swaminathan R, Chin RK, Lao TT, Mak YT, Panesar NS, Cockram CS. Thyroid function in hyperemesis gravidarum. Acta Endocrinol (Copenh) 1989; 120(2): 155-60. [CrossRef]
28. Onuora C, Maharajan G, Singh A, Etta KM. Thyroid status in various degrees of protein-calorie malnutrition in children. Clin Endocrinol (Oxf) 1983; 18(1): 87-93. [CrossRef]
29. Kelly G. Peripheral metabolism of thyroid hormones: a review. Altern Med Rev 2000; 5(4): 306-33.
30. Mebis L, van den Berghe G. The hypothalamus-pituitary-thyroid axis in critical illness. Neth J Med 2009; 67(10): 332-40.
31. Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 1992; 75(5): 1333-7.
32. Leylek OA, Cetin A, Toyaksi M, Erselcan T. Hyperthyroidism in hyperemesis gravidarum. Int J Gynaecol Obstet 1996; 55(1): 33-7. [CrossRef]
33. Hershman JM, Lee HY, Sugawara M, Mirell CJ, Pang XP, Yanagisawa M, et al. Human chorionic gonadotropin stimulates iodide uptake, adenylate cyclase, and deoxyribonucleic acid synthesis in cultured rat thyroid cells. J Clin Endocrinol Metab 1988; 67(1): 74-9. [CrossRef]