# At serum hCG concentrations >400,000 IU/L, TSH is consistently suppressed, and hCG concentrations >200,000 do not lead to symptoms of hyperthyroidism

Lockwood CM, Grenache DG, Gronowski AM. Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 2009;19:863-8.

## SUMMARY

**BACKGROUND** When serum human chorionic gonadotropin (hCG) concentrations are highest in pregnancy, there is a transient suppression of serum thyrotropin (TSH) concentrations. Although serum TSH generally remains within the nonpregnant reference intervals, in some cases TSH is suppressed, raising questions about hyperthyroidism and hyperemesis gravidarum. The aims of this study were first, to determine whether there is an hCG concentration above which serum TSH levels are suppressed to <0.2 μIU/ml; second, to determine how thyroid hormone concentrations change in response to hCG concentrations; and third, to study the clinical symptoms in patients with hCG concentrations >200,000 IU/L.

**METHODS** This is a collaborative cohort study between Washington University, Barnes–Jewish Hospital (BJH) in St. Louis, and the University of North Carolina (UNC) Hospitals in Chapel Hill. Residual blood specimens sent to the BJH and UNC laboratories for physician-ordered hCG testing were used. The goal was to accrue at least 60 women into the study with hCG concentrations >200,000 IU/L and a specimen volume sufficient for additional measurements of TSH and free thyroxine ($FT_4$).

**RESULTS** A total of 15,597 physician-ordered hCG tests were performed at BJH and UNC over a 26-month period and a 13-month period, respectively. Of this group, 69 specimens (0.4%) were from 63 women with hCG concentrations >200,000 IU/L. The medical records of 63 patients revealed that 23 (37%) had hyperemesis gravidarum (HGD) and 12 (19%) had gestational trophoblastic disease (GTD), including benign and malignant hydatidiform mole as well as choriocarcinoma with or without hCG. The remaining 28 patients (44%) were pregnant women with threatened abortion (n = 10), vaginal bleeding or spotting (n = 9), abdominal pain (n = 3), but had a normal intrauterine pregnancy (n = 6). Of the total population, 6 of 63 (10%) were pregnant with twins and one had a threatened abortion (Figure 1). None of the subjects had a prior diagnosis of hyperthyroidism. Gestational ages ranged from 4 to 20 weeks. Five subjects with a serum hCG >200,000 IU/L on more

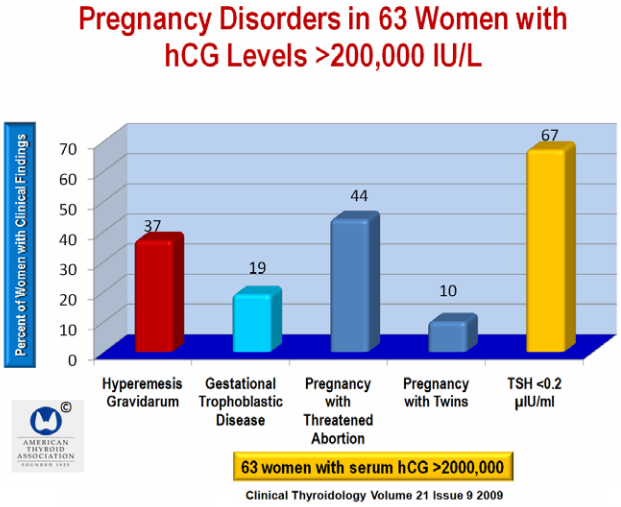
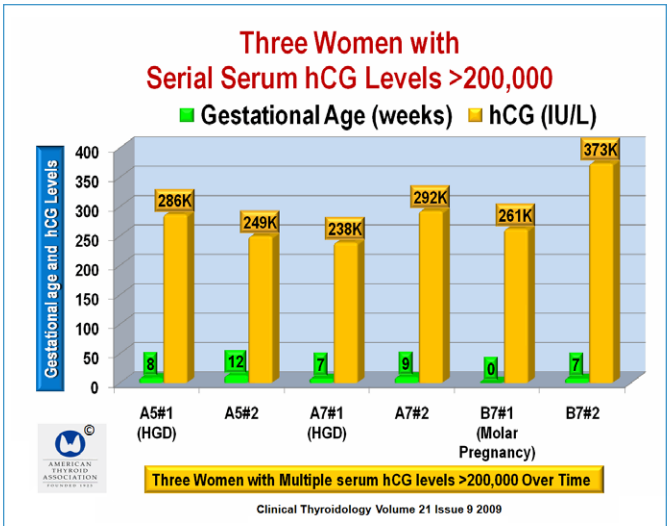
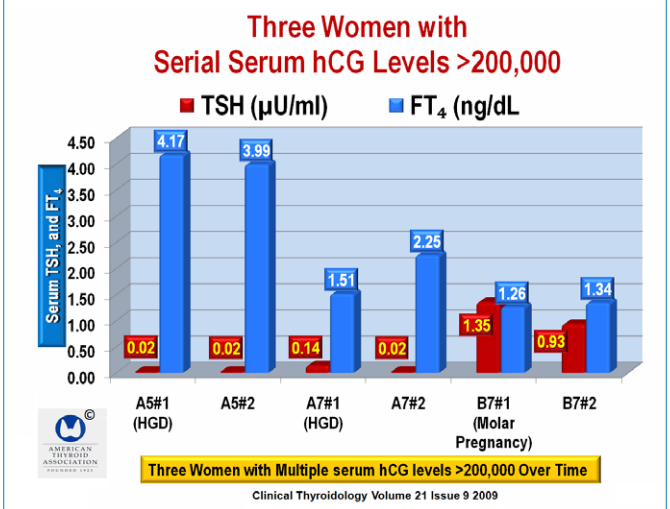



**Figure 1.** This figure shows the pregnancy disorders in 63 women with serum hCG levels >200,000 IU/L.




**Figures 2A and 2B.** These figures show serum hCG and thyroid hormone concentrations and the clinical history in three women with serial serum hCG levels >200,000 IU/L. The data for these figures are derived from Table 3 of Lockwood et al.

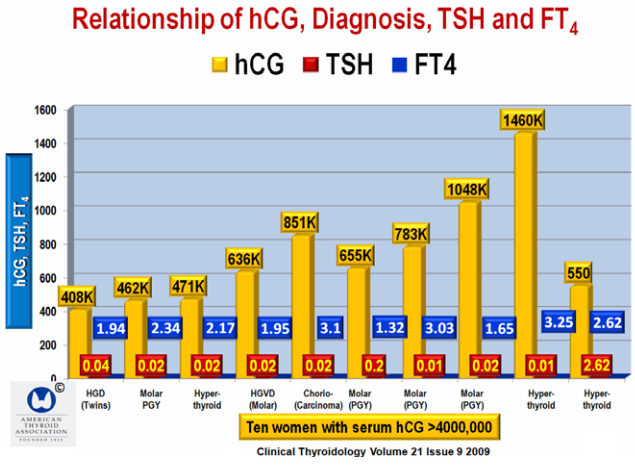



**Figure 3.** This figure shows serum levels of TSH, $FT_4$, and hCG in 10 women with serum hCG concentrations >400,000 IU/L. The figure shows the relationship of serum hCG and thyroid hormone concentrations and clinical history in 10 Specimens from 10 women with serum hCG greater than 400,000 IU/L. HGD = hyperemesis gravidarum; PGY = pregnancy. Here and in the other figures hCG is shown as 408K = 408,000. The data for this figure are derived from Table 1 of Lockwood et al.

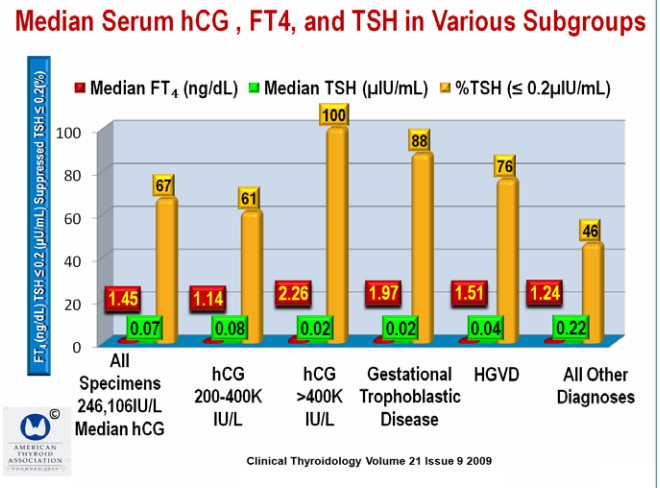



**Figure 4.** This figure shows median $FT_4$ levels, TSH levels, and the percentage of serum TSH levels ≤0.2 μIU/ml in various subgroups. HGD = hyperemesis gravidarum. The data for this figure are derived from Table 2 of Lockwood et al.

than one occasion, demonstrating how thyroid hormone levels change in response to changing hCG concentrations (Figure 2).

Among the 10 specimens with hCG concentrations >400,000 IU/L, 100% had serum TSH levels ≤2 μIU/ml and 90% had TSH levels <0.05 μIU/ml. Among the 10 specimens with an hCG concentration >400,000 IU/L, 7 were from women with molar pregnancies, 1 was from a woman with choriocarcinoma, and 2 were from pregnancies with HGD (Figure 3). Only 23 (33%) of the 69 specimens had $FT_4$ levels above the reference interval. Among the specimens with serum hCG concentrations >400,000 IU/L, only 8 of 10 (80%) had an $FT_4$ concentration >1.8 ng/dL, and of the 2 subjects with normal $FT_4$ concentrations, 1 had choriocarcinoma, with the greatest TSH concentration of 0.20 μIU/ml among specimens with hCG concentrations >400,000 IU/L. In another subject with a complete molar pregnancy, the $FT_4$ level was within the normal reference range, but was 1.65 ng/dl with a concurrent TSH level suppressed to <0.02 μIU/ml. Median serum TSH and $FT_4$ concentrations for the entire study population and subgroups with serum hCG concentrations <400,000 IU/L are shown in Figure 4. Although there were differences in $FT_4$ concentrations, clinical signs and symptoms of hyperthyroidism were noted in only 4 of 63 subjects (6%) 2 of whom had hCG concentrations >400,000 IU/L.

Median serum TSH and $FT_4$ concentrations for women with GTD was half that of the hCG group and 10-fold less that of the non-GTD and non-hCG patients. Moreover, median hCG concentrations were nearly twofold those in women with GTD than the median hCG concentrations for women with hCG or other diagnoses. In all, 80% of women with GTD had suppressed TSH concentrations <0.2 μIU/ml. Of the 69 specimens, 22 (32%) had both low TSH and elevated $FT_4$ concentrations.

**CONCLUSION** At hCG concentrations >400,000 IU/L, TSH is consistently suppressed, serum $FT_4$ and TSH respond to changes in serum hCG levels, and most patients with hCG concentrations >200,000 do not have symptoms of hyperthyroidism.

## COMMENTARY

This study is a significant contribution to the literature showing that patients with very high serum hCG levels due to trophoblastic tumors or hyperemesis gravidarum have suppressed TSH and elevated free $T_4$ concentrations. Among the 69 serum samples with hCG >200,000 IU/ml, 46 (67%) had TSH <0.2 μIU/ml and 23 (33%) had an elevated $FT_4$ level. Yet, only 4 patients had a clinical diagnosis of hyperthyroidism. The lack of clinical hyperthyroidism in many patients with trophoblastic tumors and high concentrations of hCG was reported over 30 years ago by Sidney Ingbar and his colleagues (1, 2). In contrast with these reports, Higgins et al. reported several patients with hydatidiform mole who had hyperthyroidism that was very severe both biochemically and clinically (3, 4). The serum hCG is generally less in patients with hyperemesis gravidarum than in those with trophoblastic tumor. In 57 women with hyperemesis gravidarum, Goodwin et al. noted that 60% had subnormal serum TSH levels and 45% had increased $FT_4$ levels, but none had any clinical features of hyperthyroidism (5). Their mean serum hCG level of about 100 IU/ml was threefold higher than that of a matched control group at 10 weeks of gestation. The serum hCG correlated with increased thyroid-stimulating activity in a bioassay.

The thyroid-stimulating activity of hCG measured by bioassay was reported over 30 years ago (6). HCG has about $10^4$ the activity of TSH. This thyrotropic activity depends on at least two factors: (1) the composition of hCG, which is a heterogeneous

molecule because it has variable carbohydrate composition, and (2) the TSH receptor and thyroid gland response of the host. Thirty percent of hCG is carbohydrate, more than any other glycoprotein hormone. When the sialic acid content of hCG is decreased, its thyrotropic potency is increased (7), but loss of sialic acid reduces its half-life in serum, thus decreasing its bioactivity in the host (8).

What is the potential explanation for the absence of characteristic features of hyperthyroidism in patients with high hCG and suppressed TSH? For the thyrotropic activity of hCG to have clinical consequences in these patients, the high levels of hCG must persist for several weeks, the patient must perceive symptoms, and the physician who examines the patient must do a thorough evaluation of possible features of hyperthyroidism and record them appropriately. It is not uncommon for patients with overt biochemical hyperthyroidism to deny having most of the typical symptoms and signs, even when there is some evidence that the disease has been present for several months. Symptoms in young patients are easily perceived when the hyperthyroidism is severe, but not when it is mild.

Excessive secretion of hCG causes a spectrum of thyroid dysfunction varying from suppressed TSH with no clinical features to mild hyperthyroidism detected by very careful clinical evaluation to flagrant hyperthyroidism. The variability of the thyrotropic potency of hCG depends on its carbohydrate composition, and this cannot be determined in conventional immunoassays. The potency of the thyrotropin together with the patient's response to it determines the clinical features. The variability of these two factors may explain the apparent paradox of biochemical hyperthyroidism without the usual clinical symptoms and signs in trophoblastic thyrotoxicosis.

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