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2009

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### Recommended Citation

Lockwood, Christina M.; Grenache, David G.; and Gronowski, Ann M., "Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations." *Thyroid*. 19,8. 869-868. (2009).

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# Serum Human Chorionic Gonadotropin Concentrations Greater than 400,000 IU/L Are Invariably Associated with Suppressed Serum Thyrotropin Concentrations

Christina M. Lockwood,<sup>1</sup> David G. Grenache,<sup>2,3</sup> and Ann M. Gronowski<sup>1</sup>

**Background:** During pregnancy, when human chorionic gonadotropin (hCG) concentrations are highest, there is a transient suppression of serum thyrotropin (TSH). In normal pregnancy, TSH concentrations generally remain within nonpregnant reference intervals; however, in some patients TSH is suppressed. Here we sought to extend previous studies to examine the relationship between very high serum concentrations of hCG (>200,000 IU/L) and the thyroid hormones TSH and free thyroxine (FT<sub>4</sub>). The objective of this study was to determine: 1) if there is an hCG concentration above which TSH concentrations are suppressed ( $\leq 0.2 \mu\text{IU/mL}$ ); 2) how thyroid hormone concentrations change in response to changes in hCG concentrations; and 3) the clinical symptoms in patients with such extremely elevated hCG concentrations.

**Methods:** Residual specimens sent to the laboratories for physician-ordered hCG testing were utilized. Over 26 months, 15,597 physician-ordered hCG tests were performed. Sixty-nine specimens from 63 women with hCG concentrations >200,000 IU/L were identified, and TSH and FT<sub>4</sub> concentrations were measured. Medical records were reviewed for clinical information.

**Results:** Thirty-seven percent of subjects had hyperemesis gravidarum (HG) and 19% had gestational trophoblastic disease (GTD). TSH was suppressed ( $\leq 0.2 \mu\text{IU/mL}$ ) in 67% of the specimens with hCG concentrations >200,000 IU/L and 100% of specimens with hCG concentrations >400,000 IU/L. FT<sub>4</sub> concentrations were elevated above the reference interval (1.8 ng/dL) in 32% of specimens with hCG concentrations >200,000 IU/L and in 80% of specimens with hCG concentrations >400,000 IU/L. Only four subjects had documented signs of hyperthyroidism. Women with GTD had a median hCG concentration twofold higher than women with HG and a median TSH concentration one half that of women with HG.

**Conclusions:** 1) At hCG concentrations >400,000 IU/L, TSH is consistently suppressed; 2) serum FT<sub>4</sub> and TSH respond to changes in serum hCG concentrations; and 3) most patients with hCG concentrations >200,000 IU/L lack overt hyperthyroid symptoms.

## Introduction

THE ASSOCIATION BETWEEN ELEVATED human chorionic gonadotropin (hCG) and suppressed thyrotropin (TSH) concentrations during pregnancy has been known for many years (1,2). Numerous studies have documented the thyrotropic effect of hCG (1,3–9) and in 1995, Kosugi and Mori (10) demonstrated that hCG can bind TSH receptors and suppress TSH production.

In normal pregnancy, TSH suppression is a transient phenomenon and TSH concentrations generally remain within nonpregnant reference intervals; however, in some women, TSH may be suppressed below the nonpregnant reference interval (11,12). Glinoeer (13) has proposed that, in order to trigger excessive production of thyroid hormones, circulating concentrations of hCG would need to exceed 50,000–75,000 IU/L for an extended period of time (i.e., longer than 1 week) (13). This threshold was calculated from a prospective study

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This work was presented in a poster at the American Association for Clinical Chemistry meeting, July 2009.

correlating hCG, TSH, and free thyroxine (FT<sub>4</sub>) in pregnant women, in which a 10,000 IU/L hCG increase corresponded to a mean FT<sub>4</sub> increase of 0.1 ng/dL and a mean TSH decrease of 0.1  $\mu$ IU/mL (2). Consequently, the most often cited value for serum hCG potentially exerting thyrotropic action is >50,000 IU/L. In a preliminary study, we found that ~40% (19/50) of subjects with hCG concentrations >50,000 IU/L have suppressed ( $\leq 0.2 \mu$ IU/mL) serum TSH concentrations (14). In addition, we have reported that if there is an hCG concentration above which all serum TSH concentrations can be expected to be suppressed, it is >330,000 IU/L (14). However, our study was limited because it contained very few specimens with hCG concentrations >200,000 IU/L ( $n = 18$ ).

Recently, Haddow *et al.* (15) examined the relationship between hCG and the thyroid hormones TSH and hCG in 9562 women being screened for aneuploidy (15). They reported a weak correlation between hCG and TSH in both first and second trimesters. They found that TSH was suppressed when the ratio of hCG to TSH was  $\geq 200,000$ . They also found that women with higher baseline TSH are less likely to experience suppressed TSH at any hCG concentration. Unfortunately, only a small number of their subjects had hCG concentrations >200,000 IU/L and only about five were >300,000 IU/L.

Here we sought to extend previous studies by us and others to examine the relationship between very high serum concentrations of hCG (>200,000 IU/L) and the thyroid hormones TSH and FT<sub>4</sub>. In particular, the three specific aims were to determine: 1) if there is an hCG concentration above which TSH concentrations were consistently suppressed to  $\leq 0.2 \mu$ IU/mL; 2) how thyroid hormone concentrations change in response to changes in hCG concentrations; and 3) the clinical symptoms in patients with hCG concentrations >200,000 IU/L. This information is important so that clinicians can be familiar with the expected biochemical and clinical findings in patients with such extremely elevated hCG concentrations. To our knowledge, this is the largest study of its kind.

## Materials and Methods

### Study subjects

This study was 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, North Carolina. Residual specimens sent to the BJH and UNC laboratories for physician-ordered hCG testing were utilized. Our goal was to accrue at least 60 female subjects with hCG >200,000 IU/L for which sufficient specimen volume was available for additional measurements of TSH and FT<sub>4</sub>. Medical records were reviewed for each subject to establish the subject's clinical thyroid status and document the presence of molar, trophoblastic, or other abnormal pregnancy. This study received approval from the Institutional Review Board of each institution.

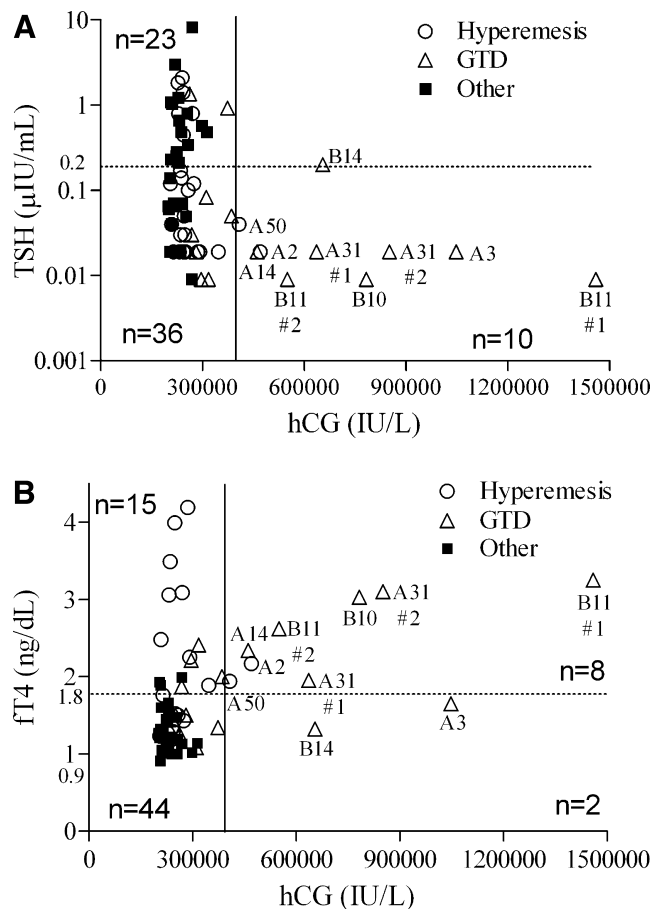
### Hormone analysis

Physician-ordered hCG testing was performed upon receipt of the specimen in the laboratory. Specimens with hCG >200,000 IU/L were refrigerated for  $\leq 3$  days before TSH and FT<sub>4</sub> testing was performed. The concentrations of serum hCG,

TSH, and FT<sub>4</sub> were measured at BJH by chemiluminescence on a Siemens Advia Centaur (Siemens Medical Solutions Diagnostics, Tarrytown, NY). At UNC, concentrations of hCG were determined by the hCG +  $\beta$  assay on a Roche Elecsys<sup>®</sup> 2010 (Roche Diagnostics, Indianapolis, IN) immunoassay analyzer and concentrations of TSH and FT<sub>4</sub> were determined using the Ortho Vitros ECI (Ortho-Clinical Diagnostics, Rochester, NY) according to the manufacturer's instructions. The hCG methods have been extensively characterized previously; both assays recognize hyperglycosylated hCG, hCG $\beta$ , and nicked hCG (16). The dynamic range of each assay was as follows: Siemens Centaur TSH = 0.02–150  $\mu$ IU/mL, FT<sub>4</sub> = 0.1–12 ng/dL; Ortho Vitros ECI TSH = 0.01–100  $\mu$ IU/mL, FT<sub>4</sub> = 0.0–6.99 ng/dL.

## Results

In order to obtain at least 60 subjects with serum hCG concentrations >200,000 IU/L, 15,597 physician-ordered hCG tests were performed at the two institutions (9777 at BJH and 5820 at UNC) over a 26-month period at BJH and a 13-month



**FIG. 1.** Scatter plots of the relationship between serum human chorionic growth hormone (hCG) and (A) thyrotropin (TSH) and (B) free thyroxine (FT<sub>4</sub>) concentrations in 69 specimens from 63 women. Dotted horizontal lines represent the TSH cutoff of 0.2  $\mu$ IU/mL and upper reference interval for FT<sub>4</sub> of 1.8 ng/dL. Vertical line represents hCG concentration of 400,000 IU/L.

TABLE 1. SERUM HUMAN CHORIONIC GONADOTROPIN AND THYROID HORMONE CONCENTRATIONS AND CLINICAL HISTORY IN TEN SPECIMENS FROM EIGHT WOMEN WITH SERUM HUMAN CHORIONIC GONADOTROPIN GREATER THAN 400,000 IU/L

| Study ID | Gestational age         | hCG (IU/L) | TSH ( $\mu$ IU/mL) | FT <sub>4</sub> (ng/dL) | Clinical history                         |
|----------|-------------------------|------------|--------------------|-------------------------|--|
| A50      | 5 weeks                 | 408,000    | 0.04               | 1.94                    | Hyperemesis gravidarum<br>Twin gestation |
| A14      | 18 weeks                | 462,000    | <0.02              | 2.34                    | Molar pregnancy<br>Hyperthyroid symptoms |
| A2       | 9 weeks                 | 471,000    | <0.02              | 2.17                    | Hyperemesis gravidarum                   |
| A31 #1   | 7 weeks                 | 636,000    | <0.02              | 1.95                    | Molar pregnancy                          |
| A31 #2   | 8 weeks                 | 851,000    | <0.02              | 3.10                    |  |
| B14      | N/A                     | 655,000    | 0.20               | 1.32                    | Choriocarcinoma                          |
| B10      | N/A                     | 783,000    | <0.01              | 3.03                    | Molar pregnancy                          |
| A3       | 20 weeks                | 1,048,000  | <0.02              | 1.65                    | Molar pregnancy                          |
| B11 #1   | N/A                     | 1,460,000  | <0.01              | 3.25                    | Molar pregnancy<br>Hyperthyroid symptoms |
| B11 #2   | 1 day after specimen #1 | 550,015    | <0.01              | 2.62                    |  |

N/A, not available.

period at UNC. Of those, 0.4% of specimens (69/15,597) from 63 women with serum hCG concentration >200,000 IU/L were identified ( $n=55$  specimens from 52 women at BJH;  $n=14$  specimens from 11 women at UNC). Review of the subjects' medical records revealed that of the 63 subjects, 37% (23/63) were diagnosed with hyperemesis gravidarum (HG) and 19% (12/63) had gestational trophoblastic disease (GTD), including benign and malignant conditions of hydatidiform mole as well as choriocarcinoma with or without HG. The remaining 44% (28/63) of patients were pregnant women presenting with threatened abortion ( $n=10$ ), vaginal bleeding/spotting ( $n=9$ ), abdominal pain ( $n=3$ ), or other reason but had normal intrauterine pregnancy ( $n=6$ ). Ten percent of the total population (6/63) was pregnant with twins (five of which had HG; one had a threatened abortion). No subject had a prior diagnosis of hyperthyroidism noted in her medical records. Gestational ages ranged from 4 to 20 weeks.

The relationship between serum hCG and serum thyroid hormone concentrations is shown in Fig. 1. In this population of specimens with hCG concentrations >200,000 IU/L, 67% (46/69) demonstrated a suppressed serum TSH  $\leq 0.2 \mu$ IU/mL (Fig. 1A). Among the specimens with hCG concentrations >400,000 IU/L, 100% (10/10) of serum TSH concentrations were suppressed to  $\leq 0.2 \mu$ IU/mL and 90% (9/10) were suppressed below  $0.05 \mu$ IU/mL. Of the 10 specimens with hCG

>400,000 IU/L, 7 were from women with molar pregnancies, 1 was from a woman with choriocarcinoma, and 2 were from pregnancies with HG (Table 1).

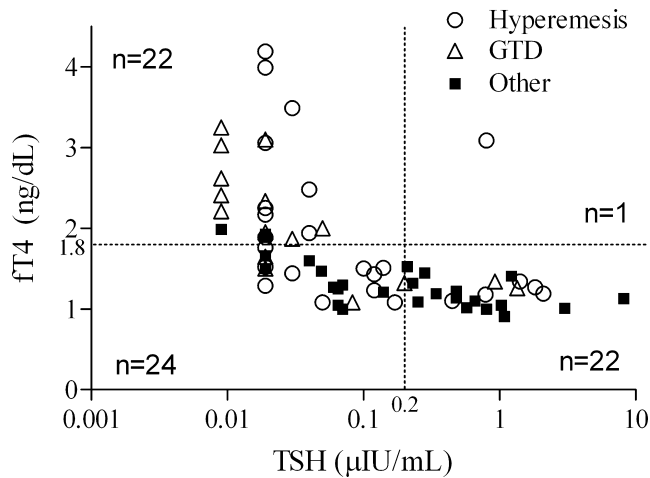
As depicted in Fig. 1B, only 33% (23/69) of the 69 specimens had elevated FT<sub>4</sub> concentrations above the reference interval (0.9–1.8 ng/dL). Among the specimens with hCG concentrations >400,000 IU/L, 80% (8/10) were >1.8 ng/dL. Of the two subjects with FT<sub>4</sub> concentrations within the normal reference intervals, one subject (B14) was diagnosed with choriocarcinoma and also exhibited the greatest TSH concentration (0.20  $\mu$ IU/mL) among specimens with hCG >400,000 IU/L. Subject A3 was diagnosed with a complete molar pregnancy and although her FT<sub>4</sub> concentration was within the normal reference interval, it was quite high at 1.65 ng/dL with a corresponding TSH suppressed to <0.02  $\mu$ IU/mL.

Median serum TSH and FT<sub>4</sub> concentrations for the entire study population and subgroups with serum hCG concentrations below or above 400,000 IU/L are shown in Table 2. There were notable differences between serum TSH and FT<sub>4</sub> concentrations in subjects with hCG concentrations >400,000 IU/L as compared to subjects with hCG concentrations between 200,000 and 400,000 IU/L. Despite these differences in thyroid hormone concentrations, clinical signs and symptoms of hyperthyroidism were noted in only 4/63 (6%) subjects, two of which had hCG concentrations >400,000 IU/L.

TABLE 2. SERUM THYROTROPIN, FREE THYROXINE, AND HUMAN CHORIONIC GONADOTROPIN CONCENTRATIONS IN VARIOUS SUBGROUPS

| Study group                       | N  | Median hCG (range) IU/L     | Median FT <sub>4</sub> (range) ng/dL | Median TSH (range) $\mu$ IU/mL | % with suppressed TSH ( $\leq 0.2 \mu$ IU/mL) |
|-----------------------------------|----|-----------------------------|--------------------------------------|--------------------------------|---|
| All specimens                     | 69 | 246,106 (200,302–1,459,892) | 1.45 (0.91–4.19)                     | 0.07 (0.01–8.15)               | 67% (46/69)                                   |
| hCG 200,000–400,000 IU/L          | 59 | 239,398 (200,302–385,305)   | 1.14 (0.91–4.19)                     | 0.08 (0.01–8.15)               | 61% (36/59)                                   |
| hCG >400,000 IU/L                 | 10 | 645,647 (407,674–1,459,892) | 2.26 (1.32–3.25)                     | 0.02 (0.01–0.20)               | 100% (10/10)                                  |
| Gestational trophoblastic disease | 16 | 423,542 (261,749–1,459,892) | 1.97 (1.08–3.25)                     | 0.02 (0.009–1.35)              | 88% (14/16)                                   |
| Hyperemesis gravidarum            | 25 | 243,970 (205,798–470,816)   | 1.51 (1.08–4.19)                     | 0.04 (0.019–2.09)              | 76% (19/25)                                   |
| All other diagnoses               | 28 | 226,155 (200,302–313,408)   | 1.24 (0.91–1.99)                     | 0.22 (0.009–8.15)              | 46% (13/28)                                   |

Nonpregnant reference intervals: TSH = 0.35–5.5  $\mu$ IU/mL; FT<sub>4</sub> = 0.9–1.8 ng/dL.



**FIG. 2.** Scatter plot of the relationship between serum TSH and FT<sub>4</sub> concentrations in 69 specimens from 63 women with hCG concentrations >200,000 IU/mL. Dotted lines represent the TSH cutoff of 0.2  $\mu$ IU/mL and upper reference interval for FT<sub>4</sub> of 1.8 ng/dL. GTD, gestation trophoblastic disease; other, non-GTD and non-hyperemesis patients.

Median serum TSH and FT<sub>4</sub> concentrations for women with GTD and HG are also shown in Table 2. The median TSH concentration of the GTD group was half that of the HG group and 10-fold less than non-GTD and non-HG patients. In addition, median hCG concentrations were nearly two times greater in women with GTD than the median hCG concentrations for women with HG or other diagnoses. Eighty-eight percent of women with GTD demonstrated suppressed TSH concentrations  $\leq$ 0.2  $\mu$ IU/mL.

The relationship between serum TSH and FT<sub>4</sub> in subjects with hCG concentrations >200,000 IU/L is shown in Fig. 2. These data demonstrate the expected inverse relationship between TSH and FT<sub>4</sub>. Of the 69 specimens, 32% (22/69) had both low TSH and elevated FT<sub>4</sub>.

Five subjects were found with serum hCG >200,000 IU/L on more than one occasion and therefore multiple measurements on a single subject were captured in the study, allowing us to assess how thyroid hormones change in response to changing hCG concentrations. Two subjects (A31 and B11) are shown in Table 1. The laboratory results for the other three subjects (A5, A7, and B7) are shown in Table 3. The hCG concentration of subject A31, who was diagnosed with a complete molar pregnancy (Table 1), increased 215,000 IU/L

(34%) over 5 days. Correspondingly, the FT<sub>4</sub> increased from 1.95 to 3.1 ng/dL (59%), while the TSH remained <0.02  $\mu$ IU/mL. One week after the mole was removed, the subject's hCG concentration had decreased to 7597 IU/L with a corresponding decrease in the FT<sub>4</sub> concentration to within the reference interval (1.5 ng/dL), though the TSH remained suppressed (<0.02  $\mu$ IU/mL). The hCG concentration of subject B11 decreased 62% in a single day following molar removal with a 19% decrease in FT<sub>4</sub> (3.25 to 2.62 ng/dL) in that same time period. The hCG concentration of subject A5, who was diagnosed with HG, decreased by 37,000 IU/L (13%) in the 5 weeks separating the laboratory measurements and a corresponding decrease in FT<sub>4</sub> concentration was observed from 4.19 to 3.99 ng/dL (4%) while the TSH remained <0.02  $\mu$ IU/mL. Another subject with HG (A7) demonstrated a 54,000 IU/L (23%) increase in hCG concentration over 10 days and, over that period, the FT<sub>4</sub> concentration increased from 1.51 to 2.25 ng/dL (49%) and TSH decreased from 0.14 to <0.02  $\mu$ IU/mL (>86%). Subject B7, diagnosed with a complete hydatidiform mole, exhibited an hCG concentration increase of 112,000 IU/L (43%) in 1 week with a 6% increase in FT<sub>4</sub> and a corresponding 31% decrease in TSH concentration (1.35 to 0.925  $\mu$ IU/mL).

### Comment

Here, we sought to determine whether a threshold serum hCG concentration exists above which serum TSH concentration can be expected to be suppressed to  $\leq$ 0.2  $\mu$ IU/mL 100% of the time. In subjects with hCG concentrations >200,000 IU/L, serum TSH was suppressed in 67% (46/69) of specimens and serum FT<sub>4</sub> was elevated above the reference interval (1.8 ng/dL) in 33% (23/69) of specimens. Among the specimens with hCG concentrations >400,000 IU/L, 100% (10/10) of serum TSH concentrations were suppressed  $\leq$ 0.2  $\mu$ IU/mL and 80% (8/10) of serum FT<sub>4</sub> concentrations were elevated >1.8 ng/dL.

What causes hCG to have thyrotropic effects in some women but not others is not clear. Some have proposed that it is due to the absolute hCG concentration (1,13). Others have suggested that the length of time hCG is elevated plays a role (13). Still others have suggested that differences in hCG glycosylation or sialylation that is seen in patients with GTD and HG results in increased thyrotropic activity (6,17–20). In the present study, it is clear that absolute hCG concentrations are higher in women with GTD. Women with GTD also demonstrated much lower TSH concentrations with 88% of GTD patients having suppressed TSH  $\leq$ 0.2  $\mu$ IU/mL. It is unclear

**TABLE 3.** SERUM HUMAN CHORIONIC GONADOTROPIN AND THYROID HORMONE CONCENTRATIONS AND CLINICAL HISTORY IN THREE WOMEN WITH SERIAL SERUM HUMAN CHORIONIC GONADOTROPIN GREATER THAN 200,000 IU/L

| Study ID | Gestational age          | hCG IU/L | TSH $\mu$ IU/mL | FT <sub>4</sub> ng/dL | Clinical history       |
|----------|--------------------------|----------|-----------------|-----------------------|------------------------|
| A5 #1    | 8 weeks                  | 286,000  | <0.02           | 4.17                  | Hyperemesis gravidarum |
| A5 #2    | 12 weeks                 | 249,000  | <0.02           | 3.99                  |                        |
| A7 #1    | 7 weeks                  | 238,000  | 0.14            | 1.51                  | Hyperemesis gravidarum |
| A7 #2    | 9 weeks                  | 292,000  | <0.02           | 2.25                  |                        |
| B7 #1    | N/A                      | 261,749  | 1.35            | 1.26                  | Molar pregnancy        |
| B7 #2    | 7 days after specimen #1 | 373,680  | 0.93            | 1.34                  |                        |

from this study if length of hCG elevation or hCG variant also played a role in the thyrotropic activities. However, it is clear that patients with GTD are at a higher risk for hCG concentrations >400,000 IU/L, suppressed TSH, and clinically apparent hyperthyroidism.

Haddow *et al.* (15) reported that in their population of 9562 pregnant women TSH was substantially suppressed when the ratio of hCG to TSH was  $\geq 200,000$ . In our study, 88% (61/69) of specimens had hCG/TSH ratios >200,000. Of these, 74% (45/61) had TSH concentrations <0.2  $\mu$ IU/mL. In our population, specimens with TSH concentrations <0.2  $\mu$ IU/mL ( $n = 45$ ) had hCG/TSH ratios  $\geq 1.4$  million.

This study identified five subjects with more than one specimen with hCG concentration >200,000 IU/L (shown in Tables 1 and 3). Although the number of these subjects was limited, they further illustrate the relationship between hCG and the thyroid hormones. As hCG concentrations changed, in all cases TSH and FT<sub>4</sub> changed in a predictable manner, with FT<sub>4</sub> changing more rapidly than TSH.

The majority of women in our study (94%, 59/63) did not have any overt signs or symptoms of hyperthyroidism reported in their medical record. Only two subjects with GTD (A14, B11) exhibited signs of hyperthyroidism with peak hCG concentrations of 462,000 and 1,460,000 IU/L respectively (Table 1). The clinical history, physical signs, and laboratory data for these two subjects were all compatible with hyperthyroidism. This data supports the idea that clinical symptoms should take precedence over biochemical measurements in these patients.

One limitation of this study is that each subject was not carefully examined for subtle signs of hyperthyroidism. However, medical records were reviewed with attention to heart rate, blood pressure, and any other signs of hyperthyroidism. It is possible that subtle signs and symptoms were missed, but clearly these subjects were clinically euthyroid when evaluated.

In this group of subjects with extremely elevated hCG concentrations (>200,000 IU/L), the inverse relationship between TSH and FT<sub>4</sub> was similar to that found in hCG-negative subjects. It is interesting to note that of the 46 specimens in our study with suppressed TSH, 48% (22/46) had normal FT<sub>4</sub> concentrations. This likely reflects the well-known log-linear relationship between TSH and FT<sub>4</sub> whereby small changes in FT<sub>4</sub> produce large changes in TSH (21).

Recently, the FaSTER Research Consortium reported the need for gestational age-specific reference intervals for TSH and FT<sub>4</sub> (22). In that study of nearly 10,000 subjects, the lower 5th centile for TSH in the first trimester was shown to be 0.13  $\mu$ IU/mL and the upper 95th centile for FT<sub>4</sub> in the first trimester was 1.38 ng/dL. Applying these cutoffs to the population described here, 90% (9/10) of subjects with hCG concentrations >400,000 IU/L demonstrated suppressed TSH and elevated FT<sub>4</sub> concentrations. Only one subject (B14) with a choriocarcinoma did not demonstrate abnormal thyroid hormone concentrations.

This study examined the physiological relationship between extremely high serum concentrations of hCG (>200,000 IU/L) and thyroid hormones. We have demonstrated that: 1) at hCG concentrations >400,000 IU/L, TSH is consistently suppressed <0.2  $\mu$ IU/mL; 2) serum FT<sub>4</sub> and TSH concentrations change as expected in response to changes in serum hCG concentrations; and 3) most patients with extremely elevated hCG concen-

trations have no overt signs and symptoms of hyperthyroidism despite altered thyroid hormone measurements.

### Acknowledgments

The authors thank Curt Parvin for assistance with data analysis and Christopher McCudden for sample analysis. We also thank the medical technologists and laboratory personnel at each institution that helped in specimen retrieval, testing, and data collection.

### Disclosure Statement

The authors declare that no competing financial interests exist.

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