Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations

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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,1 David G. Grenache,2,3 and Ann M. Gronowski1

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 (>400,000 IU/L) and the thyroid hormones TSH and free thyroxine (FT4). The objective of this study was to determine: 1) if there is an hCG concentration above which TSH concentrations are suppressed (<0.2 µIU/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 FT4 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 (<0.2 µIU/mL) in 67% of the specimens with hCG concentrations >200,000 IU/L and 100% of specimens with hCG concentrations >400,000 IU/L. FT4 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 FT4 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). Glinoer (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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concentrating hCG, TSH, and free thyroxine (FT₄) in pregnant women, in which a 10,000 IU a mean FT4 increase of 0.1 ng
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 (<0.2 µIU/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 re-
ported 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 ≥200,000. They also found
that women with higher baseline TSH are less likely to ex-
perience suppressed TSH at any hCG concentration. Un-
fortunately, 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 con-
centrations of hCG (>200,000 IU/L) and the thyroid hormones TSH and FT₄. In particular, the three specific aims
were to determine: 1) if there is an hCG concentration above
which TSH concentrations are consistently suppressed to
<0.2 µIU/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 clini-
cians 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 sub-
jects with hCG >200,000 IU/L for which sufficient specimen
volume was available for additional measurements of TSH
and FT₄. 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 Institu-
tional Review Board of each institution.

Hormone analysis

Physician-ordered hCG testing was performed upon re-
cipient of the specimen in the laboratory. Specimens with hCG
>200,000 IU/L were refrigerated for ≤3 days before TSH and
FT₄ testing was performed. The concentrations of serum hCG,
TSH, and FT₄ were measured at BJH by chemiluminescence
on a Siemens Advia Centaur (Siemens Medical Solutions Di-
agnostics, Tarrytown, NY). At UNC, concentrations of hCG
were determined by the hCG + β assay on a Roche Elecsys
2010 (Roche Diagnostics, Indianapolis, IN) immunoassay
and concentrations of TSH and FT₄ were determined
using the Ortho Vitros ECI (Ortho-Clinical Diagnostics, Ro-
chester, NY) according to the manufacturer’s instructions. The
hCG methods have been extensively characterized previously;
both assays recognize hyperglycosylated hCG, hCGβ, and
nicked hCG (16). The dynamic range of each assay was as
follows: Siemens Centaur TSH = 0.02–150 µIU/mL, FT₄ = 0.1–
12 ng/dL; Ortho Vitros ECI TSH = 0.01–100 µIU/mL, FT₄ =
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) thyroto-
pin (TSH) and (B) free thyroxine (FT₄) concentrations in 69
specimens from 63 women. Dotted horizontal lines represent
the TSH cutoff of 0.2 µIU/mL and upper reference interval
for FT₄ of 1.8 ng/dL. Vertical line represents hCG concentra-
tion of 400,000 IU/L.
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 ≤0.2 µIU/mL (Fig. 1A). Among the specimens with hCG concentrations >400,000 IU/L, 100% (10/10) of serum TSH concentrations were suppressed to ≤0.2 µIU/mL and 90% (9/10) were suppressed below 0.05 µIU/mL. Of the 10 specimens with 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 HG (Table 1).

As depicted in Fig. 1B, only 33% (23/69) of the 69 specimens had elevated FT₄ 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 FT₄ concentrations within the normal reference intervals, one subject (B14) was diagnosed with choriocarcinoma and also exhibited the greatest TSH concentration (0.20 µIU/mL) among specimens with hCG >400,000 IU/L. Subject A3 was diagnosed with a complete molar pregnancy and although her FT₄ concentration was within the normal reference interval, it was quite high at 1.65 ng/dL with a corresponding TSH suppressed to <0.02 µIU/mL.

Median serum TSH and FT₄ 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 FT₄ 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 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

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Gestational age</th>
<th>hCG (IU/L)</th>
<th>TSH (µIU/mL)</th>
<th>FT₄ (ng/dL)</th>
<th>Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>A50</td>
<td>5 weeks</td>
<td>408,000</td>
<td>0.04</td>
<td>1.94</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td>A14</td>
<td>18 weeks</td>
<td>462,000</td>
<td>&lt;0.02</td>
<td>2.34</td>
<td>Twin gestation</td>
</tr>
<tr>
<td>A2</td>
<td>9 weeks</td>
<td>451,000</td>
<td>&lt;0.02</td>
<td>2.17</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>A31 #1</td>
<td>7 weeks</td>
<td>636,000</td>
<td>&lt;0.02</td>
<td>1.95</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td>A31 #2</td>
<td>8 weeks</td>
<td>851,000</td>
<td>&lt;0.02</td>
<td>3.10</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>B14</td>
<td>N/A</td>
<td>655,000</td>
<td>0.20</td>
<td>1.32</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>B10</td>
<td>N/A</td>
<td>783,000</td>
<td>&lt;0.01</td>
<td>3.03</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>A3</td>
<td>20 weeks</td>
<td>1,048,000</td>
<td>&lt;0.02</td>
<td>1.65</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>B11 #1</td>
<td>N/A</td>
<td>1,460,000</td>
<td>&lt;0.01</td>
<td>3.25</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>B11 #2</td>
<td>1 day after specimen #1</td>
<td>550,015</td>
<td>&lt;0.01</td>
<td>2.62</td>
<td>Hyperthyroid symptoms</td>
</tr>
</tbody>
</table>

N/A, not available.

Table 2. Serum Thyrotropin, Free Thyroxine, and Human Chorionic Gonadotropin Concentrations in Various Subgroups

<table>
<thead>
<tr>
<th>Study group</th>
<th>N</th>
<th>Median hCG (range) IU/L</th>
<th>Median FT₄ (range) ng/dL</th>
<th>Median TSH (range) µIU/mL</th>
<th>% with suppressed TSH (≤0.2 µIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All specimens</td>
<td>69</td>
<td>246,106 (200,302–1,459,892)</td>
<td>1.45 (0.91–4.19)</td>
<td>0.07 (0.01–8.15)</td>
<td>67% (46/69)</td>
</tr>
<tr>
<td>hCG 200,000–400,000 IU/L</td>
<td>59</td>
<td>239,398 (200,302–385,305)</td>
<td>1.14 (0.91–4.19)</td>
<td>0.08 (0.01–8.15)</td>
<td>61% (36/59)</td>
</tr>
<tr>
<td>hCG &gt;400,000 IU/L</td>
<td>10</td>
<td>645,647 (407,674–1,459,892)</td>
<td>2.26 (1.32–3.25)</td>
<td>0.02 (0.01–0.20)</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>Gestational trophoblastic disease</td>
<td>16</td>
<td>423,542 (261,749–1,459,892)</td>
<td>1.97 (1.08–3.25)</td>
<td>0.02 (0.009–1.35)</td>
<td>88% (14/16)</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
<td>25</td>
<td>243,970 (205,798–470,816)</td>
<td>1.51 (1.08–4.19)</td>
<td>0.04 (0.019–2.09)</td>
<td>76% (19/25)</td>
</tr>
<tr>
<td>All other diagnoses</td>
<td>28</td>
<td>226,155 (200,302–313,408)</td>
<td>1.24 (0.91–1.99)</td>
<td>0.22 (0.009–8.15)</td>
<td>46% (13/28)</td>
</tr>
</tbody>
</table>

Nonpregnant reference intervals: TSH = 0.35–5.5 µIU/mL; FT₄ = 0.9–1.8 ng/dL.
Median serum TSH and FT4 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 <0.2 μIU/mL.

The relationship between serum TSH and FT4 in subjects with hCG concentrations >200,000 IU/L is shown in Fig. 2. These data demonstrate the expected inverse relationship between TSH and FT4. Of the 69 specimens, 32% (22/69) had both low TSH and elevated FT4.

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 hydatidiform mole, exhibited an hCG concentration increase of 112,000 IU/L (43%) in 1 week with a 6% increase in FT4 and a corresponding 31% decrease in TSH concentration (1.35 to 0.925 μIU/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 ≤0.2 μIU/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 FT4 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 ≤0.2 μIU/mL and 80% (8/10) of serum FT4 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 (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 ≤0.2 μIU/mL. It is unclear

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Gestational age</th>
<th>hCG (IU/L)</th>
<th>TSH (μIU/mL)</th>
<th>FT4 (ng/dL)</th>
<th>Clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5 #1</td>
<td>8 weeks</td>
<td>286,000</td>
<td>&lt;0.02</td>
<td>4.17</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td>A5 #2</td>
<td>12 weeks</td>
<td>249,000</td>
<td>&lt;0.02</td>
<td>3.99</td>
<td></td>
</tr>
<tr>
<td>A7 #1</td>
<td>7 weeks</td>
<td>238,000</td>
<td>0.14</td>
<td>1.51</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td>A7 #2</td>
<td>9 weeks</td>
<td>292,000</td>
<td>&lt;0.02</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>B7 #1</td>
<td>N/A</td>
<td>261,749</td>
<td>1.35</td>
<td>1.26</td>
<td>Molar pregnancy</td>
</tr>
<tr>
<td>B7 #2</td>
<td>7 days after specimen #1</td>
<td>373,680</td>
<td>0.93</td>
<td>1.34</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 2. Scatter plot of the relationship between serum TSH and FT4 concentrations in 69 specimens from 63 women with hCG concentrations >200,000 IU/mL. Dotted lines represent the TSH cutoff of 0.2 μIU/mL and upper reference interval for FT4 of 1.8 ng/dL. GTD, gestation trophoblastic disease; other, non-GTD and non-hyperemesis patients.
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 ≥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 µIU/mL. In our population, specimens with TSH concentrations <0.2 µIU/mL (n = 45) had hCG/TSH ratios ≥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 FT4 changed in a predictable manner, with FT4 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 FT4 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 FT4 concentrations. This likely reflects the well-known log-linear relationship between TSH and FT4 whereby small changes in FT4 produce large changes in TSH (21).

Recently, the FaSTER Research Consortium reported the need for gestational age-specific reference intervals for TSH and FT4 (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 µIU/mL and the upper 95th centile for FT4 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 FT4 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 µIU/mL; 2) serum FT4 and TSH concentrations change as expected in response to changes in serum hCG concentrations; and 3) most patients with extremely elevated hCG concentrations have no overt signs and symptoms of hyperthyroidism despite altered thyroid hormone measurements.

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Disclosure Statement

The authors declare that no competing financial interests exist.

References


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