

Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2009

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

Christina M. Lockwood

Washington University School of Medicine in St. Louis

David G. Grenache

University of North Carolina at Chapel Hill

Ann M. Gronowski

Washington University School of Medicine in St. Louis

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

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).
https://digitalcommons.wustl.edu/open_access_pubs/2836

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

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 (>200,000 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 ($\leq 0.2 \mu\text{IU/mL}$); 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 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 ($\leq 0.2 \mu\text{IU/mL}$) in 67% of the specimens with hCG concentrations >200,000 IU/L and 100% of specimens with hCG concentrations >400,000 IU/L. 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). Glinioer (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

¹Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri.

²Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

³Current address: Department of Pathology, University of Utah Health Sciences Center, Salt Lake City, Utah.

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

correlating hCG, TSH, and free thyroxine (FT₄) in pregnant women, in which a 10,000 IU/L hCG increase corresponded to a mean FT₄ increase of 0.1 ng/dL and a mean TSH decrease of 0.1 μ 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 FT₄. 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 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 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 ≤ 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 Diagnostics, Tarrytown, NY). At UNC, concentrations of hCG were determined by the hCG + β assay on a Roche Elecsys[®] 2010 (Roche Diagnostics, Indianapolis, IN) immunoassay analyzer and concentrations of TSH and FT₄ 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 β , and nicked hCG (16). The dynamic range of each assay was as follows: Siemens Centaur TSH = 0.02–150 μ IU/mL, FT₄ = 0.1–12 ng/dL; Ortho Vitros ECI TSH = 0.01–100 μ IU/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

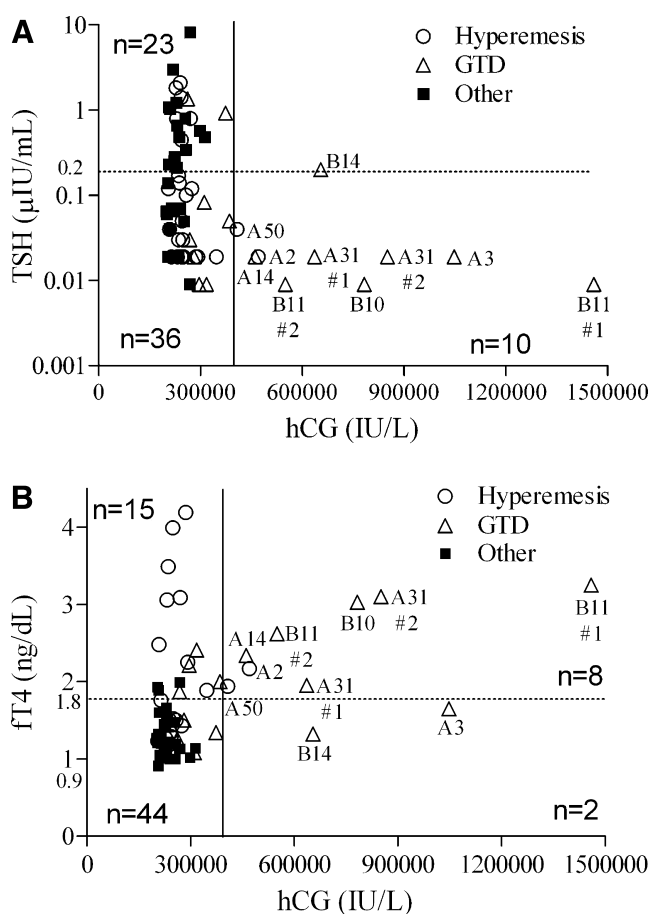


FIG. 1. Scatter plots of the relationship between serum human chorionic growth hormone (hCG) and (A) thyrotropin (TSH) and (B) free thyroxine (FT₄) concentrations in 69 specimens from 63 women. Dotted horizontal lines represent the TSH cutoff of 0.2 μ IU/mL and upper reference interval for FT₄ of 1.8 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 (μ IU/mL)	FT ₄ (ng/dL)	Clinical history
A50	5 weeks	408,000	0.04	1.94	Hyperemesis gravidarum
A14	18 weeks	462,000	<0.02	2.34	Twin gestation
A2	9 weeks	471,000	<0.02	2.17	Molar pregnancy
A31 #1	7 weeks	636,000	<0.02	1.95	Hyperthyroid symptoms
A31 #2	8 weeks	851,000	<0.02	3.10	Hyperemesis gravidarum
B14	N/A	655,000	0.20	1.32	Molar pregnancy
B10	N/A	783,000	<0.01	3.03	Choriocarcinoma
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
B11 #2	1 day after specimen #1	550,015	<0.01	2.62	Hyperthyroid symptoms

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 0.05μ 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 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 μ IU/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 μ IU/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 2. SERUM THYROTROPIN, FREE THYROXINE, AND HUMAN CHORIONIC GONADOTROPIN CONCENTRATIONS IN VARIOUS SUBGROUPS

Study group	N	Median hCG (range) IU/L	Median FT ₄ (range) ng/dL	Median TSH (range) μ 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 μ IU/mL; FT₄ = 0.9–1.8 ng/dL.

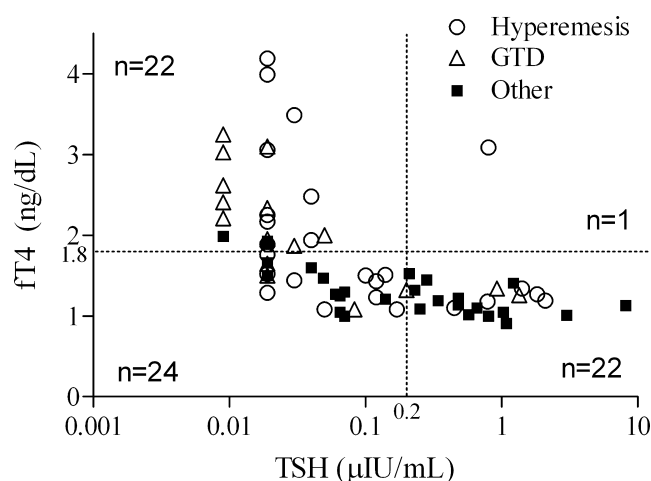


FIG. 2. Scatter plot of the relationship between serum TSH and FT_4 concentrations in 69 specimens from 63 women with hCG concentrations $>200,000$ IU/mL. Dotted lines represent the TSH cutoff of $0.2 \mu\text{IU/mL}$ and upper reference interval for FT_4 of 1.8 ng/dL . GTD, gestation trophoblastic disease; other, non-GTD and non-hyperemesis patients.

Median serum TSH and FT_4 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 $\leq 0.2 \mu\text{IU/mL}$.

The relationship between serum TSH and FT_4 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_4 . Of the 69 specimens, 32% (22/69) had both low TSH and elevated FT_4 .

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_4 increased from 1.95 to 3.1 ng/dL (59%), while the TSH remained $<0.02 \mu\text{IU/mL}$. 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_4 concentration to within the reference interval (1.5 ng/dL), though the TSH remained suppressed ($<0.02 \mu\text{IU/mL}$). The hCG concentration of subject B11 decreased 62% in a single day following molar removal with a 19% decrease in FT_4 (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_4 concentration was observed from 4.19 to 3.99 ng/dL (4%) while the TSH remained $<0.02 \mu\text{IU/mL}$. 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_4 concentration increased from 1.51 to 2.25 ng/dL (49%) and TSH decreased from 0.14 to $<0.02 \mu\text{IU/mL}$ ($>86\%$). 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_4 and a corresponding 31% decrease in TSH concentration (1.35 to $0.925 \mu\text{IU/mL}$).

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 $\leq 0.2 \mu\text{IU/mL}$ 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_4 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 $\leq 0.2 \mu\text{IU/mL}$ and 80% (8/10) of serum FT_4 concentrations were elevated $>1.8 \text{ ng/dL}$.

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 $\leq 0.2 \mu\text{IU/mL}$. 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 $\mu\text{IU/mL}$	FT_4 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 μ IU/mL. In our population, specimens with TSH concentrations <0.2 μ IU/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 μ IU/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 μ IU/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 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.

References

- Guillaume J, Schussler GC, Goldman J 1985 Components of the total serum thyroid hormone concentrations during pregnancy: high free thyroxine and blunted thyrotropin (TSH) response to TSH-releasing hormone in the first trimester. *J Clin Endocrinol Metab* **60**:678–684.
- Glinoe D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B 1990 Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab* **71**:276–287.
- Goodwin TM, Hershman JM 1997 Hyperthyroidism due to inappropriate production of human chorionic gonadotropin. *Clin Obstet Gynecol* **40**:32–44.
- Yoshikawa N, Nishikawa M, Horimoto M, Yoshimura M, Sawaragi S, Horikoshi Y, Sawaragi I, Inada M 1989 Thyroid-stimulating activity in sera of normal pregnant women. *J Clin Endocrinol Metab* **69**:891–895.
- Yoshimura M, Hershman JM, Pang XP, Berg L, Pekary AE 1993 Activation of the thyrotropin (TSH) receptor by human chorionic gonadotropin and luteinizing hormone in Chinese hamster ovary cells expressing functional human TSH receptors. *J Clin Endocrinol Metab* **77**:1009–1013.
- Yoshimura M, Pekary AE, Pang XP, Berg L, Goodwin TM, Hershman JM 1994 Thyrotropic activity of basic isoelectric forms of human chorionic gonadotropin extracted from hydatidiform mole tissues. *J Clin Endocrinol Metab* **78**:862–866.
- Tomer Y, Huber GK, Davies TF 1992 Human chorionic gonadotropin (hCG) interacts directly with recombinant human TSH receptors. *J Clin Endocrinol Metab* **74**:1477–1479.
- Ball R, Freedman DB, Holmes JC, Midgley JE, Sheehan CP 1989 Low-normal concentrations of free thyroxine in serum in late pregnancy: physiological fact, not technical artefact. *Clin Chem* **35**:1891–1896.
- Davies TF, Platzer M 1986 hCG-induced TSH receptor activation and growth acceleration in FRTL-5 thyroid cells. *Endocrinology* **118**:2149–2151.
- Kosugi S, Mori T 1995 TSH receptor and LH receptor. *Endocr J* **42**:587–606.
- Glinoe D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S 1993 Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest* **16**:881–888.
- Grun JP, Meuris S, De Nayer P, Glinoe D 1997 The thyrotrophic role of human chorionic gonadotrophin (hCG) in the early stages of twin (versus single) pregnancies. *Clin Endocrinol (Oxf)* **46**:719–725.

13. Glinioer D 1997 The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* **18**:404–433.
14. Riley J, Moore, JL, Gronowski, AM 2006 The relationship between serum human chorionic gonadotropin and the thyroid hormones thyroid stimulating hormone and free T₄. Presented at the 2006 AACC Annual Meeting. *Clin Chem* **52**(6 Suppl):A97.
15. Haddow JE, McClain MR, Lambert-Messerlian G, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME; First and Second Trimester Evaluation of Risk for Fetal Aneuploidy Research Consortium 2008 Variability in thyroid-stimulating hormone suppression by human chorionic gonadotropin during early pregnancy. *J Clin Endocrinol Metab* **93**:3341–3347.
16. Cole LA, Sutton JM, Higgins TN, Cembrowski GS 2004 Between-method variation in human chorionic gonadotropin test results. *Clin Chem* **50**:874–882.
17. Tsuruta E, Tada H, Tamaki H, Kashiwai T, Asahi K, Takeoka K, Mitsuda N, Amino N 1995 Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. *J Clin Endocrinol Metab* **80**:350–355.
18. Jordan V, Grebe SK, Cooke RR, Ford HC, Larsen PD, Stone PR, Salmond CE 1999 Acidic isoforms of chorionic gonadotropin in European and Samoan women are associated with hyperemesis gravidarum and may be thyrotrophic. *Clin Endocrinol (Oxf)* **50**:619–627.
19. Talbot JA, Lambert A, Anobile CJ, McLoughlin JD, Price A, Weetman AP, Robertson WR 2001 The nature of human chorionic gonadotropin glycoforms in gestational thyrotoxicosis. *Clin Endocrinol (Oxf)* **55**:33–39.
20. Kato K, Mostafa MH, Mann K, Schindler AE, Hoermann R 2004 The human chorionic gonadotropin molecule from patients with trophoblastic diseases has a high thyrotropic activity but is less active in the ovary. *Gynecol Endocrinol* **18**:269–277.
21. Spencer CA, LoPresti JS, Patel A, Guttler RB, Eigen A, Shen D, Gray D, Nicoloff JT 1990 Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. *J Clin Endocrinol Metab* **70**:453–460.
22. Lambert-Messerlian G, McClain M, Haddow JE, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME; FaSTER Research Consortium 2008 First- and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. *Am J Obstet Gynecol* **199**:62 e1–6.

Address correspondence to:

Ann M. Gronowski, Ph.D.

Department of Pathology and Immunology

Washington University School of Medicine

660 S. Euclid, Box 8118

St. Louis, MO 63110

E-mail: gronowski@wustl.edu