Are women at an increased risk of gestational thyrotoxicosis?

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ABSTRACT

Objectives: To evaluate the relative importance of thyroid hormones and human chorionic gonadotropin in relation to the risk of gestational thyrotoxicosis in Saudi women living in Jeddah, Kingdom of Saudi Arabia.

Methods: A prospective study was conducted on Saudi healthy pregnant women (N=406) at 12-15 weeks of gestation and compared with healthy non-pregnant controls (N=200). Maternal serum levels of free thyroxine free triiodothyronine, thyrotropin, human chorionic gonadotropin and free β-human chorionic gonadotropin together with urinary iodine excretion were determined. Analysis of variance was used to examine differences among the groups for different variables and the Bonferroni criterion was used when significance tests were made.

Results: Pregnant women were classified into 2 groups according to the lower limit of serum thyrotropin levels in non-pregnant euthyroid controls at ≥ 0.3 mIU/L (Group one) or < 0.30 mIU/L (Group 2). Suppressed levels of serum thyrotropin (< 0.30 mIU/L) were found in 11.1% of pregnant women which was accompanied by significant increases in free thyroxine (P<0.001), free triiodothyronine (P < 0.05), human chorionic gonadotropin (P<0.001) and β-human chorionic gonadotropin (P<0.001). A significant negative correlation between serum levels of thyrotropin and that of human chorionic gonadotropin (r=-0.381, P<0.001) was observed. The relative risk of having a serum thyrotropin level of < 0.30 mIU/L was 4.89 (P<0.001) for the pregnant women examined as compared with non-pregnant controls. Approximately 5.6% of the women examined exhibited biochemical evidence of thyrotoxicosis.

Conclusion: The results of the present study show that Saudi pregnant women are at risk of developing biochemical evidence of thyrotoxicosis during early gestation, and thus, are likely to be at greater risk of clinically evident gestational thyrotoxicosis and hyperemesis gravidarum. Genetically determined differences in the synthesis or metabolism of human chorionic gonadotropin isoforms, or both may contribute to this increased risk.

Keywords: Thyroid function, gestational thyrotoxicosis, hyperemesis gravidarum, human chorionic gonadotropin.

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The physiological activation of the normal thyroid in early pregnancy has been attributed partly to the stimulus by thyrotropin (TSH) like effects of human chorionic gonadotrophin (hCG), due to structural similarity to TSH.[1-3] Increased sialylation mediated by estrogens can diminish thyroxine-binding globulin (TBG) clearance leading to increases in total thyroxine (T4) and tri-iodothyronine (T3).[2] Changes in the levels of albumin and free fatty acids can influence the extent of thyroid hormones binding to carrier proteins, and thus, decreasing circulating levels of free T4 (FT4) and free T3 (FT3) as pregnancy progresses.[4] In some pregnant women, excessive stimulation by hCG leads

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to transient increase in thyroid hormone levels, hyperemesis gravidarum (HG), and other clinical signs which, were recently coined as "gestational thyrotoxicosis" (GT).[5-6] However, the relationship between the changes in hCG, thyroid hormones and GT is complex. The exact etiological mechanisms leading to HG is not fully understood. It is possible that HG is caused by hyperthyroidism,[7] hyperstimulation by hCG[8] or other unknown mechanism(s) or both. Bouillon et al[9] showed that 70% of hyperemetic women exhibited increased FT4 index, whereas Bober et al[10] found that 40% of the women examined exhibited an increased FT4 and an impaired TSH response to thyroliberin (TRH). However, Evans et al[11] reported no evidence to support the involvement of hCG in inducing morning sickness through its thyrotropic effects on the thyroid gland. Furthermore, Goddwin et al[5] concluded that biochemical hyperthyroidism and vomiting were 2 separate events.

Recent studies have demonstrated increased risk of developing GT in Asian women during the first trimester of pregnancy as compared with their corresponding Caucasian counterparts.[12] Similar finding were reported in Chinese women living in Hong Kong.[13] However, ethnic origins were not generally described in other studies on GT.[1,5] No information is available in the literature on the extent of GT in Saudi pregnant women, and therefore, the main objective of the present study is to evaluate the frequency of biochemical thyrotoxicosis in Saudi pregnant women, living in Jeddah, Kingdom of Saudi Arabia (KSA), during the first trimester of gestation. In addition, the interactions between hCG and TSH together with other thyroid function tests are examined. The results are discussed in relation to the regulatory mechanism(s) involved in the control of thyroid function during the first trimester of gestation.

Subjects. A total of 406 Saudi pregnant women living in the Jeddah area participated in the present study. Age and anthropometric data of the women studied are presented in **Table 1.** All women had resided in the Jeddah area for more than 5 years and were recruited from antenatal clinics at King Abdulaziz University Hospital (KAUH) and New Jeddah Clinic Hospital (NJCH), Jeddah, (KSA). Women with hepatic, renal or with evident endocrine disorders, with a history of immunosuppresive therapy or with a history of thyroid dysfunction or on any form of drug treatment were excluded from the study. In addition, all pregnant women included were: 1. Screened negative for both anti-thyroperoxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg); and 2. Not smoking cigarette or shessha. The group was studied at presentation to the antenatal clinics (range 12-15 weeks gestation, mean ± standard deviation (SD) 13.52 ± 1.45 weeks). At the first appointment, all pregnant women had a general physical and obstetric examination and measurements of their height and weight were made. In addition, they underwent an ultrasound scan in order to confirm the pregnancy and assess fetal age and maturity. At the visit blood samples were collected for the measurement of FT4, FT3, TSH, hCG and β-hCG. Urinary iodine (UI) excretion was also determined in urine samples collected at the visit.

At birth all newborns were examined for the following observations: 1. Apgar score, birth-weight, head-circumference and fetal length; 2. Birth weight centile; which were determined using locally developed birth weight standards;[14] 3. Pediatric estimation of pregnancy age and its correlation with gestational age estimated by ultrasound and from menstrual data; 4. The presence of any congenital malformations; and 5. Complications at birth.

A total of 200 non-pregnant Saudi women who were randomly selected also participated in the present study, as a reference population for comparative purposes. They were healthy and were not lactating and had not been lactating during the previous 2 years, were not pregnant and had not been pregnant during the previous 2 years, were not using oral contraceptives, and had regular menstrual cycles. The mean (± SD) age was 27.3 ± 4.6 years and mean body mass index (BMI) 23.22 ± 1.66 kg/m^2.

Methods. Maternal bloods together with urine samples were collected. Also samples were collected from non-pregnant women. Collected blood samples were immediately transferred to the laboratory and sera were separated by centrifugation. Collected sera and urine samples were divided into multiple aliquots and stored at –130ºC until analysis. All assays and determinations were performed in batches, to eliminate variability within assays.

Determination of free thyroxine, free triiodothyronine, thyrotropin, human chorionic gonadotropin and β-human chorionic gonadotropin. Free thyroxine, FT3, TSH, and hCG levels were determined in sera using the electrochemi-luminescence immunoassay (ECLIA) technique using Elecsys 2010 system Autoanalyzer (Boehringer Mannheim Laboratory Diagnostics, Boehringer Mannheim GmbH, D-68298 Mannheim, Germany). All the kits and reagents were obtained from the same supplier. Serum β-hCG was measured by an immunoradiometric assay (CIS, United Kingdom (UK), High Wycombe, UK). Intra- and inter-assay precisions for the various assays were indicated by the coefficients of variance (% CV), as follows: Free tyroxine (1.8% and 3.2%); FT3 (2.1% and 2.7%); TSH (1.9% and 2.5%); and hCG (3.5% and 4.6%).

Determination of urinary iodine excretion. Urinary iodine was measured by dry ashing the

samples and then estimating the catalytic effect of the I^- on the reduction of ceric ions to cerous ions in the presence of arsenous ions which were oxidized to arsenic. The change in color of the former was measured from the standard curve. Measurements were carried out in duplicates after the method of Wilson & van Zyl.[15] Recovery of added ^{125}I and ^{127}I was above 95% and not corrected for. The lower detection limit for the assay was 0.15 umol/L. The mean CV for 0.18 umol/L was 16.2%, for 0.78 umol/L was 7.1% and for 1.3 umol/L was 5.5%. Results were expressed both as microgram of iodine per gram creatinine (ug/g) or directly as umol of iodine per liter of urine (umol/L). Creatinine was measured by the standard technique described by Jaffe.[16]

Determination of anti-thyroperoxidase and anti-thyroglobulin. Anti-thyroperoxidase and Anti-Tg levels in sera were determined using coated well enzyme linked immunoassay technique by kits supplied by Diagnostic System Laboratory Inc, Webster, TX, USA.

Statistical analysis. Results are presented as means (± SD.) Data was analyzed using statistical package for social sciences (SPSS) (version 10 for Windows Smart Viewer) supplied by SPSS Inc. 2000, Mapinfo Corp. Tokyo, NY, USA. Results that were not normally distributed were log-transformed before analysis. Analysis of variance was used to examine differences among the groups for different variables, and the Bonferroni criterion was used when significance tests were made. Correlations were carried out using regression analysis.

Results. A total of 406 Saudi pregnant women were studied during the first trimester who had successful delivery of their neonates at term. Relevant clinical and anthropometric data on the mothers and neonates is presented in **Table 1.** None of the babies delivered showed any form of neonatal complications or morbidity. Based on blood sampling during the first trimester, 2 groups of pregnant women were identified according to the lower limit of serum TSH levels in non-pregnant euthyroid women defined at 0.30 mIU/L: Group one: TSH ≥ 0.30 mIU/L and Group 2: TSH < 0.30 mIU/L. The means of serum TSH, FT4, FT3, hCG, β-hCG and UI excretion in the 2 groups of pregnant women as compared to non-pregnant counterparts (Group 3) are presented in **Table 2.**

Serum TSH levels in Group one were significantly higher than that of Group 2 (P<0.0001). The distribution of serum TSH values in Groups one and 2 is shown in **Figure 1.** Serum TSH levels were significantly decreased in pregnant women during the first trimester as compared to non-pregnant group (P <0.001) with 11.1% of pregnant women of Group 2 exhibiting a 6.7-fold decrease in serum TSH levels (P < 0.0001). In addition, 5.6% of the women examined exhibited biochemical evidence of thyrotoxicosis. Both serum levels of FT4 (P<0.001) and FT3 (P<0.05) were significantly increased in women of Group 2 as compared to that of Group one. Serum hCG (P< 0.001) and β-hCG (P<0.001) levels were significantly increased in women of Group 2 as compared to that of Group one. There was no significant difference in UI excretion between women of Groups one and 2. The relative risk of having a serum TSH level of <0.30 mIU/L was 4.89 (95% confidence interval, 4.61 – 5.20; x^2 =17.5; P< 0.001) for the pregnant (45 out of 406) as compared to non-pregnant women (3 out 203) studied. The 3 non-pregnant women with TSH levels <0.30 mIU/L were excluded from the final analysis. A significant negative correlation between serum TSH and hCG levels was evident (r = -0.381, P<0.0001). There was no correlation between maternal weight and the levels of serum TSH, FT4, FT3 and hCG or FT4, FT3 and β-hCG in the women studied.

Table 1 - Maternal age, body mass index, gravida, week of delivery, fetal birth weight, fetal length, circumference of pregnant women according to thyrotropin levels (measured at the first trimester).

Variables	Group one (TSH ≥ 0.30 mIU/L) N=361	Group 2 (TSH < 0.30 mIU/L) N=45
Age (years)	26.75 ± 4.92	26.41 ± 5.38
Body mass-index (kg/m^2)	26.11 ± 4.80	25.77 ± 3.02
Gravida	4.22 ± 2.15	4.10 ± 2.64
Week of delivery	39.71 ± 1.35	39.64 ± 1.42
Fetal birth weight (g)	3395 ± 382	3384 ± 416
Fetal length (cm)	51.69 ± 3.70	51.92 ± 3.86
Fetal head circumference (cm)	34.85 ± 2.22	34.72 ± 2.13

N - number, TSH - thyrotropin
Values are presented as means ± standard deviation for 406 pregnant women at delivery

Discussion. During the first trimester of pregnancy, direct stimulation of the maternal thyroid gland by increased hCG levels has been demonstrated previously.[1,17-18] The rise in hCG is accompanied by a partial inhibition of the thyroid-pituitary axis.[18] Thus, a transient decrease in serum TSH levels corresponds with the peak values of hCG and the changes in serum TSH and hCG are mirror images of each other. In the present study, the changes in serum TSH levels in the women studied during the first trimester of pregnancy are consistent

Table 2 - Comparison of mean serum thyrotropin, free thyroxine, free triiodothyronine, human chorionic gonadotropin, β-human chorionic gonadotropin and urinary iodine excretion in Saudi pregnant women according to thyrotropin levels as compared with non-pregnant women.

Variables	Group one (TSH) ≥ 0.30 mIU/L) N=361	Group 2 (TSH < 0.30 mIU/L) N=45	Group 3 (Non-pregnant) N=200	Probability (P)
Thyrotropin (TSH) (mIU/L)	1.41 ± 0.04*	0.21 ± 0.01*	1.94 ± 0.40	0.0001
Free thyroxine (FT4) (pmol/L)	13.8 ± 1.25*	15.95 ± 1.71*	15.17 ± 1.80	0.05
Free triiodothyronine (FT3) (pmol/L	4.66 ± 0.45*	5.26 ± 0.38*	5.21 ± 0.57	0.05
Human chorionic gonadotropin (HCG) (kIU/L)	52.40 ± 2.20*	104.30 ± 5.81*	N/A	0.001
β-human chorionic gonadotropin (β-HCG) (IU/L)	12.96 ± 0.15*	20.82 ± 1.52*	N/A	0.001
Urinary iodine excretion (UI) (umol/L)	1.23 ± 0.38*	1.18 ± 0.41*	1.03 ± 0.15	0.05
(ug/g creatinine)	164.8 ± 50.5*	158.1 ± 46.2*	138.5 ± 20.6	0.05

N - number, F - probability, * - statistically significant from corresponding control values, N/A - not applicable
Values are presented as means ± standard deviation for 406 pregnant women at first trimester measurements

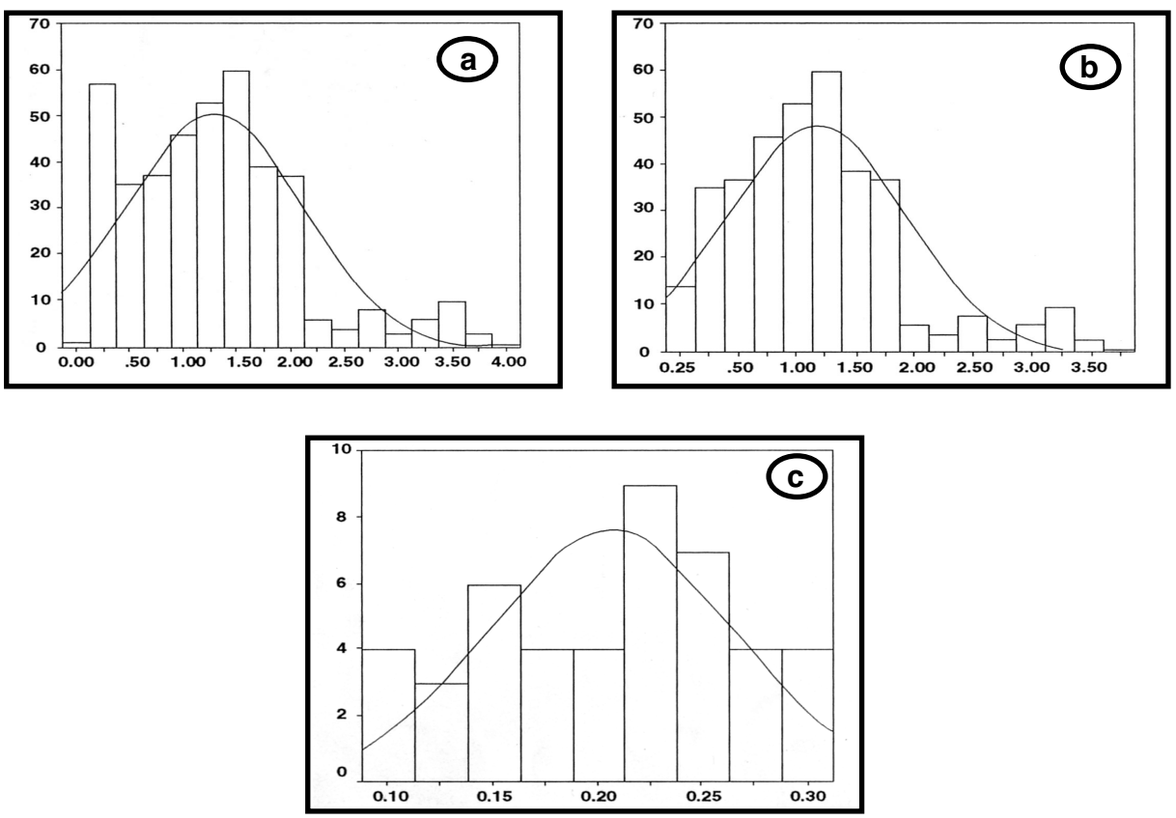

Figure 1 - Distribution of thyrotropin values in all women studied **(a)** women with thyrotropin ≥ 0.30 mU/L **(b)** women with thyrotropin < 0.30 mU/L and **(c)** with superimposed line of normal distribution.

with previous studies,[19-21] but contrasted with the work of Rasmussen et al,[22] who found no changes in TSH levels during pregnancy as compared with 12-month postpartum values. These contradictory results are partly explained by methodologies employed in the measurement of thyroid function tests, and probably by the iodine status of the population examined.[23] In the present study, 11.1% of the pregnant women (Group 2) examined between 12-15 weeks of gestation, exhibited a 6.7-fold decrease in serum TSH levels ($P<0.0001$) as compared to pregnant women (Group 1) with serum TSH levels defined at $\geq$0.30 mIU/L (mean ± SD: 1.41 ± 0.04 mIU/L). This suppression in serum TSH values in Group 2 was accompanied by the following changes: 1. A small but significant increase in the serum levels of both FT4 ($P<0.001$) and FT3 ($P< 0.05$) as compared to that of pregnant women of Group 1; 2. A significant increase in the serum levels of hCG (by 99.1%, $P<0.001$) and β-hCG (by 60.6%, $P<0.001$), and 3. A significant negative correlation between serum TSH and hCG ($r = -0.381$, $P<0.001$). The findings of the present study are similar to that described previously.[17,24] Glinoer and co-workers showed, that in approximately 20% of normal pregnant women examined, a transient lowering in serum TSH below the lower limit of reference values was evident: thus, in women with a blunted serum TSH level (defined as a lowering < 0.20 mIU/L), circulating hCG levels were significantly higher in comparison with hCG levels in 80% of the pregnancies examined, who maintained unaltered serum TSH levels.[25] In addition, a linear relationship between peak hCG and FT4 levels during the first trimester of pregnancy was evident.[25-26] The significant suppression of TSH during the first trimester was suggested to be related to ethnic differences: Panesar et al[27] demonstrated in a large study on Chinese pregnant healthy women, that 4.6% of all pregnant women examined (weeks of gestation 5-41) had suppressed serum TSH levels and 6.5% had suppression before the 25th week of gestation with 12.7% exhibiting the highest suppression during the first trimester of pregnancy, when FT4 levels were the highest. Moreover, Serum TSH was suppressed in 16% of Asian and 5% of Caucasian women living in England.[12] Also, TSH was suppressed in 9% of North American and 13% of European women studied in the first trimester of pregnancy, but the latter were not classified according to ethnic origin.[28]

There is considerable evidence supporting the suggestion that hCG causes thyroidal stimulation which occurs in vivo, when hCG levels are peaked during the first trimester and that excessive thyroidal stimulation by hCG may precipitate into GT that may manifest in some women as HG.[6,9,17,28-30] This is not surprising, since both TSH and hCG, are heterodimeric glycoproteins sharing considerable similarity in their β-subunits with a common α-subunit and similar receptors.[31-32] Further evidence to support the stimulatory effect of hCG on thyroidal function during the 1st trimester include: 1. There exists thyroid-stimulating activity (TSA) in sera of normal pregnant women, and the TSA shows a significant correlation with hCG;[33] 2. In vitro studies with hCG extracts from normal pregnant sera by means of anti-hCG monoclonal antibodies, induced cylic adenosine monophosphate (c-AMP) accumulation in fisher rat thyroid cell line-5 (FRTL-5) cells and the effect correlated with hCG immunoreactivity;[31] and 3. Human chorionic gonadotropin was shown to stimulate thyroid hormone release by human thyroid cells if these cells were allowed to form follicles.[31-32] However, other studies have shown that thyroid function tests were not related to HG[34] and attempts at hCG neutralization have not removed the TSA in sera obtained from pregnant women.[35] In addition, hCG showed little or no stimulatory effect on cAMP-production by human thyroid cells (or their membranes) interacting with TSH-receptor transfected Chinese hamster ovary cells.[31-32] These differences have been resolved recently by the observation that hCG may exist in various isoforms (or variants) which may arise from differences in C-terminal extension, or glycosylation or sialylation or both,[36] and showing considerable differences in potency. Indeed, increased sialylation, mediated by estrogens, can decrease the clearance of TBG, thus, resulting in elevated levels of T4 and T3.[2] In addition, partially sialylated (or more basic) hCG was found to be more potent in vitro as a thyroid stimulator.[17,36] Finally, purified hCG, like TSH was shown to: 1. Enhance iodide uptake and c-AMP production in FRTL-5 rat thyroid cells; and 2. Stimulate iodide uptake, organification, and T3 secretion in cultured human thyroid follicles.[31-32] The free hCG β-subunits are possibly not responsible for thyroid stimulation in pregnancy. The increase in total hCG in women of Group 2 was by far greater than than free hCG β-subunits as indicated by the change in the ratio of β-hCG/hCG. This may suggest that any subfraction responsible for stimulation of thyroid function in pregnancy is likely to be part of the whole hCG molecule rather than any subunit. Further work is needed in this regard.

The present results suggest that Saudi women are at a higher risk of developing GT, as evident by the greater extent of thyroidal stimulation during the first trimester. Supporting this, 5.6% of the women studied exhibited biochemical evidence of thyrotoxicosis, although clinical signs and symptoms were not recorded. The questions that we put forward were: What is (are) the reason(s) for this observation, and is it related to ethnic difference(s)? Currently,

the answer is unknown. One possibility is the predominance of hCG with prolonged biological activity. This could be related to the genetically determined variability in the extent of glycosylation or peptide heterogeneity of hCG or its rate of synthesis or both. The latter could be determined by the genetic make up of the Saudi women studied. Racial differences may also explain inconsistent observation on the role of thyroid hormones in HG[5,6,36] and the morning sickness of pregnancy,[11] as it is possible that non-thyroidal causes will be more common in Caucasian populations living in North America and Europe.

Recently, Jordan et al[37] and Talbot et al[38] showed that acidic isoforms of hCG may play a role in the etiology of HG and GT, and the longer half-life of acidic hCG isoforms may result in increased in vivo TSH-receptor cross-talk with resultant thyrotrophic effects. Also, Tsurura et al[39] have concluded that thyrotoxicosis with hyperemesis may be caused by circulating asialo-hCG with higher thyrotropic bioactivity. Panesar et al,[13] have suggested that hCG may causally be related to the development of HG through an indirect effect(s) on thyroid function. Finally, it is possible that hCG may be causing hyperemises via direct action on the gastrointestinal system,[40-41] but the latter possibility needs further studies.

In conclusion, the present prospective study shows that, during the first trimester of pregnancy, Saudi women are more frequently developing biochemical evidence of thyrotoxicosis and are therefore, likely to be at greater risk of clinically apparent GT.

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