Original Article

The association between serum TSH concentration whithin the normal range and nutritional status in euthyroid pregnant women at the first trimester of gestation

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Background: Follow-up studies have shown an increased risk of thyroid dysfunction in individuals with normal serum thyroid-stimulating hormone (TSH) levels. Furthermore, the possible consequences of minor differences in thyroid function (without achieving poor thyroid function) in the risk of weight gain during pregnancy are questionable, too. The production of TSH is under the hypothalamus–pituitary control, and food is one of the most effective environmental agents that control hypothalamic–pituitary–thyroid axis activity. Regarding the few available studies, we assessed the association of minor variations of TSH concentrations and nutritional status in the first trimester of pregnancy. **Materials and Methods:** This cross-sectional descriptive and analytical study was performed on 150 primiparous healthy women. Demographic and family characteristics were collected using a researcher-administered questionnaire. Nutrients intake were extracted from a 72-h recall, and physical activity scores were determined by the pregnancy physical activity scale. **Results:** The prepregnancy body mass index (BMI) (β =0.022, P = 0.004) and participants' weight at 6–10 weeks of gestation (β =0.006, P = 0.024) were positively associated with TSH concentrations, while total physical activity score was negatively correlated (β = −0.006, P = 0.047). We did not find any significant association between TSH values and energy-adjusted nutrients intake (P > 0.05). **Conclusion:** We suggest that differences in TSH concentrations within normal range in the first trimester are correlated with gaining weight, physical activity level, and prepregnancy BMI. TSH concentration and consequently thyroid function may influence on gestational weight gain or vice versa.

Key words: Iran, nutrients, pregnancy, thyroid-stimulating hormone

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INTRODUCTION

Thyroid-stimulating hormone (TSH) has become the first-line marker of thyroid function for most clinical conditions including pregnancy.[1] Serum TSH concentration endures dynamic changes throughout gestation, since the maternal thyroid gland reacts to the double challenge of the estrogen-mediated increase in T4-binding globulin, and a concurrent augmented renal iodine secretion, which the first needs

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an enhanced pool of T4, and second frequently intensified by suboptimal iodine intake.[1] During the first trimester, serum TSH concentration significantly decreases, because of the reciprocal response to direct thyroid stimulation mediated by human chorionic gonadotropin (hCG), when the hCG concentration peak is reached. Present guidelines suggest that a reference limit of 2.5 mU/L for TSH may apply throughout the first trimester of pregnancy, while some authors believe that this threshold is very limited.[2] Using a limited set of references is an unreasonable simplification that will lead to recurrent misclassifications and possibly incorrect treatment choices. Therefore, we considered a range of 0.13–4.16 mIU/L as a normal range for inclusion of pregnant women.[3] The optimal concentration of TSH in the serum for achieving physical and mental health is questionable, especially in pregnancy, and follow-up studies have shown an increased risk of thyroid dysfunction in individuals with normal serum TSH levels, while destructive effects have been reported for suppressed and particularly elevated serum TSH levels.[3-4] The possible consequences of minor differences in thyroid function (without achieving poor thyroid function) in the risk of weight gain during pregnancy are questionable, too.[5] Lifestyle is undoubtedly important for weight gain during pregnancy,[6] but interaction with other factors such as TSH hormone is not explained in detail.[7] On the other hand, the production of TSH is under the hypothalamus–pituitary control and food is one of the most effective environmental causes that control hypothalamic–pituitary–thyroid axis activity. Lartey *et al*. showed that the availability of food influences thyroid activation through not only leptin-induced thyrotropin-releasing hormone but also TSH expression and conversion of thyroxine to triiodothyronine through Type 2 diodinase in rat skeletal muscle.[8] Iodine is a main substrate for the synthesis of TSH which is derived frequently from the environment.[9] The asparagine is part of the structure of TSH which regulates communication with other hormones.[10] Vitamin A activates gene that regulates TSH, and folic acid concentrations have been linked to levels of TSH.[11,12] Animal studies have shown relationships between nutrients intake and levels of TSHs, but it is difficult to verify these associations in human populations, especially in pregnancy. In view of the above, we performed a cross-sectional study to assess the possible association between serum TSH within the normal range and nutritional status which have not been widely assessed.

MATERIALS AND METHODS

This cross-sectional descriptive and analytical study was performed on 150 primigravidas healthy aged 18–40 years in Isfahan, Iran, between June 2017 and September 2019. The study protocol was approved by the Ethics Committee of the Public Health College of Shahid Sadoughi University of Medical Sciences (IR.SSU.SPH.REC.1396.13). Inclusion criteria included gestational age between 6 and 10 weeks, a history of no smoking, Iranian by origin, and singleton pregnancy. Participants with twin or higher order multiple pregnancy, the TSH range out of the 0.13–4.16 mIU/L range,[3] medical problems affecting body weight, drug-related hypertension, Type 1 or 2 diabetes mellitus, addiction, being on special diet, chronic illness, kidney disease, and body mass index (BMI) ≥35 kg/m^2 were excluded.[13] The mentioned criteria were identified by the health-care providers and also from the participants' medical records. Based on the stratified sampling, 15 community health centers, 5 hospitals, and 15 private offices were selected for the purpose of introducing pregnant mothers to take into account the effect of participants' socioeconomic conditions on study results. At the significant level of 0.95% (α =0.05), power of 0.80% (β =0.20) and P = 0.3 as the least acceptable correlation in terms of performance, minimum sample size with a 10% drop rate was 134.[14]

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{C(r)^2} + 3$$

After obtaining written consent, demographic and family characteristics were collected using a researcher-administered questionnaire. In order to assess nutritional status, we measured prepregnancy BMI, participants' weight, weight gained at the end of the first trimester, and nutrients intake. Nutrients intake were extracted from a validated questionnaire (72-h dietary recall) by a responsible person who was not aware of the objectives of the study goals. All participants were instructed to record everything they ate for 2 consecutive days and 1 weekend day at 6–10 weeks of pregnancy. Then, responsible person estimated nutrients intake from dietary records using the Nutritionist-4 software (First Databank Inc., Hearst Corp., San Bruno, CA-Version 3.5.2). Physical activity score was determined as the confounding variable with the pregnancy physical activity scale.[15] Pregnancy Physical Activity Questionnaire (PPAQ) is a self-administered semi-quantitative questionnaire with 32 activities including household, occupational, sports, transportation, and sedentary activities. Pregnant women were trained to choose the item best assessing the quantity of time spent on an activity per day or week during the first trimester for each activity. Duration is from 0 to 6 or more per day and from 0 to 3 or more per week during the current month. The validity and reliability of PPAQ have been confirmed in Iranian women, too.[16] Participants' weights at the mentioned times were measured by a digital beam (Chinese hand weighing scale BR-9705120 Persatab Trading

Company). Serum TSH concentration was assessed by immunoradiometric assay (Kavoshyar Co., Tehran, Iran) at 6–10 weeks of pregnancy.

Statistical analysis

Data were analyzed by SPSS 20 (SPSS Inc., Chicago, Ill., IBM Corp., Armonk, NY, USA) software. The normal distribution of variables was assessed by Kolmogorov–Smirnov test. Square root transformation was used to convert TSH (dependent variable) levels into normal distribution, because the logarithmic transformed values were skewed. All nutrients intake have been adjusted for energy using the residual method. Factor analysis has been used to make all possible combinations of nutrients.[17] Mean of independent variables such as demographic data, prepregnancy BMI, participants' weight at 6–10 weeks of gestation, participants' gained weight at the end of first trimester, physical activity score, and energy adjusted nutrients intake were determined and the association of every one of them with the square root of TSH concentrations were assessed with single regression analysis. To adjust the effect of significant maternal characteristics, TSH concentration for the second order was entered into the multiple regression model as dependent variable. Then, associated characteristics (physical activity score, pregravid BMI, and gained weight in the first trimester) were simultaneously placed in the relevant box as independent variables. We compared the estimated nutrients intake with the current Recommended Dietary Allowances (The levels of intake of essential nutrients that, on the basis of scientific knowledge, are judged by the Food and Nutrition Board to be adequate to meet the known nutrient needs of practically all healthy persons) (US RDA) by one sample *t*-test.

RESULTS

Mean and standard deviation of participants' characteristics and nutrients intake have been shown in Tables 1 and 2. The mean of nutrients intake was significantly different of the RDA amounts, except linoleic acid, Vitamin A, Vitamin B3, Vitamin K, Vitamin B2, and Vitamin B12 [Table 3].

Table 1: Demographic characteristics of subjects (*n*=138)

Demographic and family characteristics	Mean (SD)	Minimum-maximum
Age (years)	26.52 (4.06)	18-39
Pregravid-BMI (kg/m^2)	23.59 (3.91)	16-35.59
Weight gain in the first trimester (kg)	1.31 (2.50)	−6.5-11
Participants' weight in the first trimester (kg)	62.60 (11.02)	39-95
Total physical activity (met/hour)	30.81 (11.65)	30.81-84.90
Education frequency, *n* (%)		
≤ Diploma	54 (39.42)	
Associate degree	14 (10.22)	
Bachelor	65 (47.44)	
Master's degree and doctorate	4 (2.92)	
Job frequency, *n* (%)		
Housewife (house keeping)	83 (60.3)	
Nongovernmental jobs	38 (27.2)	
Government jobs	17 (12.5)	
Household income frequency, *n* (%)		
<4,000,000 (Rials)	6 (4.35)	
4,000,000-6,000,000	18 (13.04)	
6,000,000-9,000,000	43 (31.16)	
9,000,000-12,000,000	41 (29.71)	
>12,000,000	30 (21.74)	

SD=Standard deviation; BMI=Body mass index

Table 2: The association between thyroid-stimulating hormone levels and participants' characteristics (*n*=138)

Variable	β	*P*	0.95% CI	β*	*P**	0.95% CI
Age	0.010	0.125	−0.003-0.022			
Education	0.046	0.067	−0.003-0.095			
Job	0.003	0.947	−0.085-0.091			
Household income	0.027	0.501	−0.053-0.108			
Total physical activity	−0.005	0.036	−0.009-0.000	−0.004	0.081	−0.009-0.001
Pregravid BMI	0.014	0.043	0.000-0.028	0.006	0.694	−0.023-0.034
Weight gain in the first trimester (kg)	0.014	0.178	−0.006-0.035			
Participants' weight in the first trimester (kg)	0.006	0.024	0.001-0.011	0.002	0.693	−0.008-0.013

*The association of significantly correlated of characteristics with TSH concentrations when they entered into multiple regression model. TSH=Thyroid stimulating hormone; BMI=Body mass index; CI=Confidence interval

Table 3: The association of energy adjusted nutrients intake and thyroid stimulating hormone values (*n*=138)

Nutrients intake/daily*	Mean (SD)	RDA of nutrients intake	*P**	β	*P***	0.95% CI for β
Energy (kcal)	1773.71 (524.07)	2400	<0.001	−0.00001	0.862	0.000-0.000
Protein (g)	62.34 (22.71)	71	<0.001	0.002	0.371	−0.002-0.006
Total fat (g)	53.47 (26.93)	65	<0.001	0.000	0.823	−0.003-0.003
Saturated fat (g)	13.59 (7.16)	<20	<0.001	0.000	0.960	−0.010-0.011
Cholesterol (mg)	163.00 (142.07)	300	<0.001	0.000055	0.837	0.000-0.001
Polly unsaturated fatty acid (g)	12.89 (9.04)	6	<0.001	−0.004	0.303	−0.013-0.004
Linoleic acid (g)	15.35 (10.88)	13	0.099	−0.000042	0.992	−0.008-0.008
Oleic acid	13.15 (9.84)	20	<0.001	0.000	0.923	−0.006-0.007
Alpha-linolenic (g)	0.14 (0.11)	2	<0.001	−0.105	0.706	−0.652-0.443
Vitamin A (mcg)	810.66 (944.93)	770	0.614	−0.000012	0.697	0.000-0.000
Vitamin E (mg)	3.75 (3.61)	15	<0.001	−0.007	0.439	−0.025-0.011
Thiamine B1 (mg)	1.63 (0.69)	1.4	<0.001	−0.064	0.384	−0.208-0.081
Vitamin B3 (mg)	17.64 (8.01)	18	0.589	0.004	0.363	−0.005-0.012
Folic acid (mcg)	204.80 (121.87)	600	<0.001	0.000	0.315	−0.001-0.000
Pantothenic acid (mg)	4.13 (3.27)	6	<0.001	−0.003	0.744	−0.020-0.014
Vitamin C (mg)	99.36 (66.46)	85	0.010	−0.000059	0.905	−0.001-0.001
Vitamin K (mcg)	85.32 (76.65)	75-90	0.408	−0.001	0.083	−0.002-0.000
Charbohydrate (g)	260.75 (90.78)	175	<0.001	−0.000097	0.882	−0.001-0.001
Glucose (g)	12.48 (8.34)			0.002	0.277	−0.003-0.013
Fructose (g)	17.90 (12.28)	55		0.003	0.342	−0.003-0.008
Lactose (g)	5.78 (5.92)	<12		0.002	0.686	−0.009-0.014
Iron (mg)	16.76 (6.78)	27	<0.001	−0.000007	0.989	−0.001-0.001
Magnesium (mg)	253.37 (183.92)	350-400	<0.001	0.000	0.302	−0.001-0.000
Manganese (mg)	2.99 (2.48)	2	<0.001	−0.008	0.605	−0.036-0.021
Zinc (mg)	6.23 (2.90)	11-12	<0.001	0.001	0.939	−0.028-0.030
Sodium (g)	1131.51 (682.88)	1.5		−0.000089	0.119	0.000-0.000
Potassium (mg)	2353.35 (1070.27)	2000	<0.001	−0.000026	0.419	0.000-0.000
Calcium (mg)	617.67 (312.09)	1000	<0.001	−0.000078	0.531	0.000-0.000
Phosphorous (g)	849.62 (403.48)	700	<0.001	−0.0001	0.290	0.000-0.000
Copper (mg)	1.36 (1.22)	1	0.001	−0.015	0.578	−0.068-0.038
Selenium (mcg)	0.07 (0.04)	60		−0.423	0.642	−2.219-1.374
Chromium (mcg)	0.04 (0.03)	30		0.486	0.668	−1.755-2.727
Molybdenum (mcg)	22.80 (27.27)	50	<0.001	−0.001	0.458	−0.003-0.001
Beta-carotene (mcg)	506.76 (986.48)	770	0.002	−0.000005	0.853	0.000-0.000
Alpha-tocopherol	4.19 (4.91)	15 mg (22.5 IU)		−0.010	0.374	−0.031-0.012
Vitamin B2 (mg)	1.54 (1.59)	1.4	0.309	−0.013	0.476	−0.047-0.022
Vitamin B6 (mg)	1.39 (0.71)	1.9	<0.001	−0.051	0.339	−0.155-0.054
Vitamin B12 (mcg)	3.12 (4.06)	2.6	0.131	−0.000081	0.991	−0.014-0.014
Vitamin B8 (mcg)	18.73 (14.04)	15	<0.001	−0.003	0.093	−0.008-0.001
Biotin (mcg)	19.50 (16.76)	30	<0.001	−0.001	0.413	−0.005-0.002
Vitamin D (mcg)	1.27 (3.46)	15	<0.001	−0.003	0.716	−0.019-0.013
Fiber (g)	16.32 (8.96)	28	<0.001	−0.001	0.857	−0.008-0.007
Sugar (g)	1.02 (1.54)	25	<0.001	−0.001	0.334	−0.002-0.001
Galactose (g)	1.53 (3.41)	3.1	<0.001	−0.014	0.860	−0.044-0.037
Caffeine (mg)	33.01 (31.60)	400	<0.001	−0.001	0.302	−0.003-0.001
Percentage calories from protein	13.19 (4.60)	12-20	0.002	0.007	0.388	−0.009-0.022
Percentage energy from carbohydrates	54.71 (16.75)	50-60	<0.001	0.000002	0.999	−0.004-0.004
Percentage energy from fat	24.95 (10.76)	30	0.835	−0.001	0.709	−0.008-0.005

*Mean and SD of un-adjusted nutrients intake; **P: The association of adjusted-nutrients intake with TSH values by single regression analysis. TSH=Thyroid stimulating hormone; SD=Standard deviation; CI=Confidence interval; RDA=Recommended dietary allowance

The pregravid BMI and participants' weight at 6–10 weeks of gestation were positively associated with TSH values, while total physical activity was negatively correlated. We did not find any significant association between TSH values and energy adjusted nutrients intake [Table 3]. After adjusting for associated characteristics, there was only a trend to significant association between physical activity and TSH concentration ($\beta = -0.004$, $P = 0.081$) [Table 2, the sixth column].

DISCUSSION

In the present study, TSH concentration was positively correlated with pregravid BMI and participants' weight at the first trimester, while it correlated negatively with total physical activity, but, failed to show significant association with energy adjusted nutrients intake in euthyroid pregnant women. Similarly, Kumar *et al*. and Sheng *et al*. concluded that TSH values were positively associated with BMI in early pregnancy among healthy pregnant women.[18,19] Leptin produced in adipose tissue affects the hypothalamus and increases TSH secretion.[20] Furthermore, the association between BMI and TSH can be hindered by hCG.[21] Nagel *et al*. reported an inverse association of TSH serum level with resting energy expenditure in euthyroid elderly subjects, too.[22] Furthermore, Ceresini *et al*. reported that even a mild thyroid hormone excess was associated with a decreased physical function in the population of elderly men.[23] Physical activity can be an alternative to the hypothalamus–adipocyte–leptin axis, resulting in increased energy flux from adipose tissue.[24] We did not find any association between energy-adjusted nutrients intake and TSH values. Similarly, another study reported that serum TSH was not dependent on food composition but reduced after caloric deprivation independent of changes in T4 and T3.[25] A literature review on 42 articles concluded that excessive or inadequate amounts of iodine aid to thyroid dysfunction. Deficiency of zinc and selenium resulting of unbalanced diet at any stage of life can lead to a decreased production of thyroid hormones.[26] However, further investigations are needed to illuminate the associations of nutrients intake and TSHs.

The present study has some limitations. First, our findings could not elucidate causal relationships and the associations that were observed could also be explained by reverse causality. Hence, we suggest further prospective studies to show and approve the causal relationship. Second, this study was confined to the pregnant women in Isfahan and it may be difficult to generalize our results to other ethnic groups. Further studies with other ethnic groups are proposed to confirm the findings. Finally, the sample size is small. Despite these limitations, we think that this is the first study to indicate the association between TSH concentration within normal limits and nutritional status in Iranian pregnant women. Furthermore, this study may help to define the reference range of thyroid hormone in early pregnancy and can be generalized to other Iranian populations. Furthermore, our findings showed that small differences in TSH within the normal range (without reaching obvious thyroid dysfunction) may influence on gestational weight gain in the first trimester, and throughout pregnancy which its prevalence is 18%–35% and is the main reason of obesity among women in reproductive ages. Finally, the association between minor variations within TSH levels and physical activity level in euthyroid pregnant women may indicate that even a relatively minor contribution to energy expenditure through TSH may be enough to increase BMI, especially in pregnant women whose physical activity have been diminished.

CONCLUSION

We suggest that differences in TSH concentrations within normal range in the first trimester are correlated with gaining weight, physical activity level, and prepregnancy BMI. TSH concentration and consequently thyroid function may influence on gestational weight gain or vice versa.

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Conflicts of interest
There are no conflicts of interest.

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