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RESEARCH ARTICLE

ASSOCIATION OF THYROID-STIMULATING HORMONE AND THYROID HORMONES, T3 AND T4 WITH LIPID PROFILE IN GHANAIAN NORMOTENSIVE PREGNANT WOMEN

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ABSTRACT

Thyroid dysfunction during pregnancy is associated with various adverse perinatal and maternal outcomes. Evidence suggests that thyroid stimulating hormone (TSH) may exert extra-thyroidal effects and modify the profile of blood lipids. Data from Ghana on thyroid hormone status and its association with lipid profile in pregnancy is scant. The aim of this was study to determine the association between maternal blood lipid profile and thyroid hormone status in normotensive pregnant women. Serum levels of thyroid stimulating hormone (TSH), thyroxine (FT4), and free triiodothyronine (FT3) in normotensive pregnant women and aged matched non-pregnant women were assayed. Total cholesterol (TC), triglyceride (TG) and high-density lipoprotein (HDL-c) cholesterol were also analyzed. TSH and FT3 levels were significantly different between the two groups, with pregnant women having lower mean TSH and higher FT3 than control subjects. Mean FT4 was not significantly different between the two groups. There was a significant positive correlation between TSH and BMI. However, the correlation between TSH and TC, TSH and TG, FT3 and TG, as well as TSH and FT3 was insignificant. Our results agree with the general consensus that changes occur in levels of TSH and thyroid hormones during pregnancy, albeit within the normal reference range. However, there is the need for gestational-age dependent reference ranges for FT3 and FT4 in the Ghanaian population to adequately assess thyroidal effects of TSH on lipid profile.

Keywords: Pregnancy, lipid, Ghanaian, thyroid status, TSH, FT4, FT3,

INTRODUCTION:

Thyroid hormones have significant functions in embryogenesis and fetal development[1,2]. It is widely recognized that thyroid function undergoes significant changes during pregnancy[3,4,5]. Both overt and sub-clinical thyroid dysfunction are known to have adverse effects on maternal and fetal outcome[6]. In the absence of primary thyroid disease, uncorrected thyroid dysfunction during gestation could have adverse fetal and perinatal outcomes. Early diagnosis and management of maternal thyroid dysfunction is therefore essential to ensure minimal fetal and perinatal adverse effects. An advance in the assessment of thyroid function during pregnancy indicates that thyroid function test interpretation depends on the stage of pregnancy[5]. In some "normal" pregnancies, TSH levels are suppressed due to very high levels of Human chrionic gonadotropin (hCG) during the first trimester. Human chrionic gonadotropin (hCG), a glycoprotein hormone secreted by placenta, shares a common alpha subunit with TSH, and acts as a weak TSH-receptor agonist[6]. hCG has a mild stimulatory effect on the thyroid, and causes a transient "physiological" elevation of FT4 and FT3[7]. TSH levels measurement at this time therefore, may not provide a good indicator of thyroid function. Later phases of gestation, it has been suggested, could be more reflective of maternal thyroid status[8]. Serum levels of thyroid hormone have been reported to be decreased, increased or unchanged during pregnancy, depending on the assay used[8]. Thyroid dysfunction in the absence of primary thyroid disease may result in various quantitative and/or qualitative changes of triglycerides, phospholipids, cholesterol, and other lipoproteins[9]. Dyslipidemia, a consequence of thyroid dysfunction, increases risk for cardiovascular disease[10,11,12]. Previous studies have shown that thyroid stimulating hormone (TSH), free thyroxine (FT4) and free

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triiodothyronine (FT3) are significantly associated with lipid profile in the euthyroid population, regardless of gender[13,14]. The influence of TSH on lipid profile has been assumed to be mediated indirectly, through its effect on thyroid hormones. However, additional evidence suggests that this association is partially contributed by the direct extra-thyroidal effect of TSH on lipid profile[15,16]. Normal pregnancy is associated with predicted changes in lipid metabolism and elevation in lipid concentration as gestation progresses[17]. However, these changes are considered to be generally non-atherogenic, and fall sharply to pre-pregnancy levels following delivery[18,19]. Advances in understanding the physiology of thyroid function in normal pregnancy have highlighted the importance of the consequences of abnormal function on obstetric outcome and fetal well-being. As to how modifications in thyroid function modulates changes in lipid profile is yet to be ascertained in a Ghanaian population. The aim of this study therefore was to determine the association between thyroid profile and circulatory lipids in Ghanaian normotensive pregnant women.

MATERIALS AND METHODS:

Subjects: 55 apparently healthy normotensive primigrvidae pregnant women attending the antenatal clinic of the Department of Gynecology, Korle-Bu Teaching Hospital, Korle-Bu and 41 age-matched apparently healthy, normotensive non-pregnant women residing in the nearby communities around Korle-Bu who tested negative for urinary β-hCG (control group) were recruited for this study. Informed consent was obtained from all participants. Women on treatment for thyroid disorders, or with a history previously diagnosed thyroid function abnormalities, as well as those on hormonal therapy were excluded from this study. For pregnant women, data on gestational age, parity, and other clinical details were collected as part of routine antenatal care and recorded. Duration of gestation was calculated from last menstrual period and verified by ultrasonography. All subjects were asked about personal and family history of thyroid disease.

Clinical and biochemical measurements:

Demographic data including age, weight, height and waist-hip ratio were collected using standard questionnaires at recruitment. Blood pressure (BP) was measured by first allowing participants to rest for 15 minutes prior to measurement. Venous blood samples were drawn after an overnight fast and distributed into serum collection tubes. Total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-c) were measured by automated enzymatic methods (Vital Scientific Microlab 300M, VSM 300). LDL-cholesterol (LDL-c) was calculated according to Friedewald formula[20]. Thyroid hormone profile (TSH, FT3 and FT4) for all subjects were assayed using enzyme-linked immunosorbent assay (ELISA), (Human, Germany) and Labsystems Multiscan-352 plate reader (Finland).

Statistical Analysis: Baseline characteristics, clinical and biochemical measurements were expressed as mean ± SD (standard deviation) for continuous variables, and as percentages for categorical variables. Student *t*-test was used to compare the mean difference of the groups using Graphpad 3.0. Pearson correlation coefficient (r) was used for interdependency of parameters and $p \leq 0.05$ was considered statistically significant for all analyses.

Ethical Approval: This study was approved by the Ethical and Protocol Review Committee of the School of Allied Health Sciences of the College of Heath Sciences, University of Ghana, Legon.

RESULTS:

Baseline characteristics and clinical parameters of the study groups are shown in Table 1.

Table 1: Baseline characteristics and clinical variables of the study groups

Parameter	Pregnant women (N= 55)	Control (N = 41)	95% CI of mean Diff.	*p*-value (t-test)
Gestation period (weeks)	33.70 ± 4.89	-	-	-
Age (yrs)	30.76 ± 4.86	31.95 ± 6.67	-3.54 - 1.16	0.3169
SBP (mmHg)	127.60 ± 20.51	118.15 ± 15.79	1.79 - 17.11	0.0162*
DSP (mm Hg)	82.32 ± 15.69	77.94 ± 10.77	-1.29 - 10.05	0.1286
BMI (kg/m^2)	32.48 ± 6.41	27.25 ± 7.58	2.38 - 8.08	0.0004*

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure. Values are presented as mean ± standard deviation. $p < 0.05$ is considered statistically significant.

Pregnant women were not significantly different from the control group with respect to age and diastolic blood pressure ($p > 0.05$). However, pregnant women had significantly higher systolic blood pressure and BMI than non-pregnant women ($p < 0.05$). For pregnant women, the mean age of gestation at recruitment was 33 weeks.

The lipid profiles of both study groups are presented in Table 2.

Table 2: Lipid profile of the study groups

Parameter	Pregnant women (N= 55)	Control (N = 41)	95% CI of mean Diff.	*p*-value (t-test)
TC (mmol/l)	4.60 ± 1.04	4.63 ± 1.26	-0.54 - 0.40	0.7675
TG (mmol/l)	1.50 ± 0.60	1.02 ± 0.53	0.25 - 0.71	0.0001*
HDL-c (mmol/l)	1.03 ± 0.23	0.97 ± 0.36	-0.05 - 0.17	0.2992
LDL-c (mmol/l)	2.89 ± 0.86	3.24 ± 1.30	-0.79 - 0.09	0.1137
TC/HDL-c	4.57 ± 0.89	4.83 ± 1.92	-0.85 - 0.33	0.3814
VLDL-c (mmol/l)	0.68 ± 0.27	0.32 ± 0.29	0.25 - 0.47	0.0001*

TC = total cholesterol; TG = triglycerides; HDL-c = high density lipoprotein cholesterol; LDL-c = low density lipoprotein cholesterol; TC/HDL-c = cardiovascular risk. Values are presented as mean ± standard deviation.
$p < 0.05$ is considered statistically significant.

Mean serum levels of TG and VLDL-c were significantly higher in pregnant women than in non-pregnant women. However, TC, HDL-c, LDL-c and cardiovascular risk were not significantly different between the two study groups ($p > 0.05$).
Thyroid hormone profiles (TSH, FT3 and FT4) for the study groups are shown in Table 3.

Table 3: Thyroid hormone profile (TSH, FT3 and FT4) for the study groups

Parameter	Pregnant women (N= 54)	Control (N = 41)	95% CI of mean Diff.	*p*-value (t-test)
TSH (MIU/ml)	1.22 ± 0.51	1.57 ± 0.96	0.04 -0.66	0.0274*
FT3 (pmol/l)	5.44 ± 0.91	5.05 ± 0.61	-0.72 - (-0.06)	0.0209*
FT4 (pmol/l)	13.27 ± 2.77	14.57 ± 5.47	-0.45 - 3.05	0.1426

TSH = thyroid stimulating hormone; FT3 = free triiodothyroxine; FT4 = thyronine. Values presented as mean ± standard deviation. $p < 0.05$ is considered statistically significant.
Serum levels of TSH and FT3 were significantly different between the two study groups. Pregnant women showed significantly reduced TSH and elevated FT3 levels when compared to non-pregnant women ($p < 0.05$). However, serum FT4 levels were not significantly different between the two study groups.
Table 4 shows the correlation between BMI, SBP, TC, TG, TSH and FT3 in pregnant women at 33 weeks of gestation.

Table 4: Correlation between BMI, SBP, TSH, FT3 TC, TG, HDL-c, LDL-c and Alb. in the pregnant women

Parameters	BMI	SBP	T. chol	TG	Alb	TSH	fT3
BMI	1.000						
SBP	-.040	1.000					
T. chol	.274	.079	1.000				
TG	.398	.076	.376	1.000			
TSH	.377	-.036	.137	.157	-.087	1.000	
fT3	-.029	-.261	.016	-.019	.068	-.150	1.000

BMI = body mass index; SBP = systolic blood pressure; Alb = Albumin; TC = total cholesterol; TG = triglycerides; TSH = thyroid stimulating hormone; FT3 = free triiodothyroxine
± .266 critical value is significant at 0.05. ± .345 critical value is significant at 0.01
BMI showed positive and significant correlation with TC ($r = 0.274$, $p < 0.05$), TG ($r = 0.398$, $p < 0.01$) and TSH ($r = 0.377$, $p < 0.01$). However, we observed a weak and negative correlation with SBP and FT3 ($p > 0.05$). SBP correlated positively with FT3, TC and TG but weakly and negatively with TSH ($p > 0.05$). TC correlated positively with TG ($r = 0.376$, $p < 0.01$)

and TSH (r = 0.137, p > 0.05) but weakly with FT3 (r = 0.016, p > 0.05). TG relationship with TSH was positive (r = 0.157, *p* >0.05) and negative with FT3 (r = -0.019, *p* > 0.05).

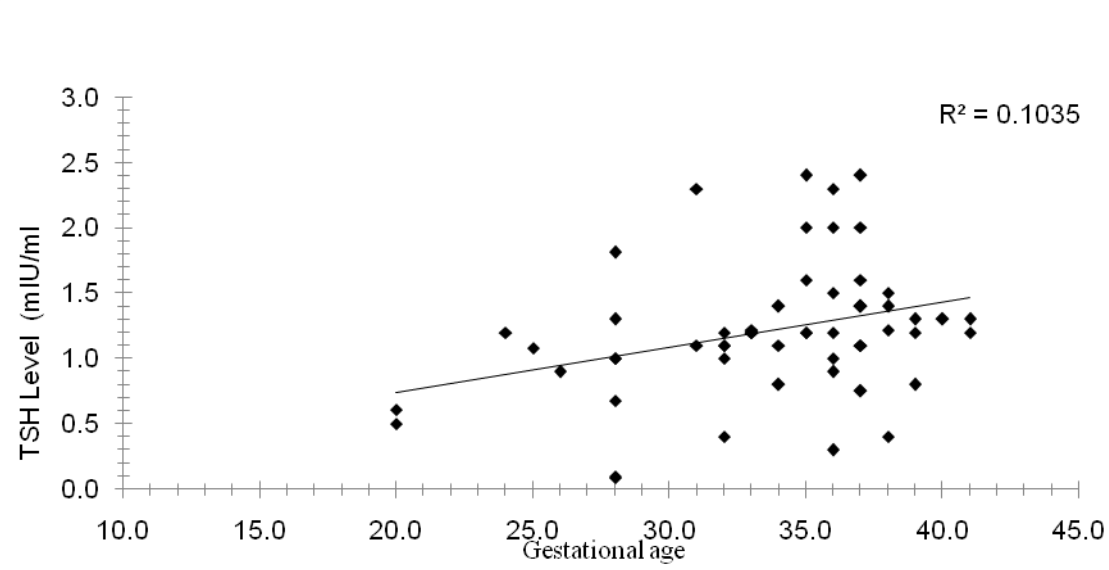

Figure 1: variation of TSH with gestational age

DISCUSSION:

Providing adequate nutrition to the growing fetus during pregnancy requires significant physiological and biochemical adjustments of various tissues and organ systems. Given that liver, muscle, kidneys are major sites of peripheral deiodination of T4 to T3, serum concentrations are likely to differ in pregnancy[21]. Compared to non-pregnant women, our results show that TG and VLDL-c were significantly elevated in apparently healthy pregnant women. This observation is supported by other studies[22,23]. A few studies have pointed to estrogen as the main modulator of elevated TG in pregnancy. Estrogen induces hepatic biosynthesis of endogenous triglycerides which is transported by VLDL[24,25]. Although our study did not reveal significant differences in mean serum levels of LDL-c and HDL-c between the two study groups, at least one study has reported significant differences in LDL-c and HDL-c levels between similar study groups, and this it is believed could be related to circulating estrogen and progesterone[25]. The significantly higher BMI with accompanying higher VLDL-c and TG we observed in pregnant women is consistent with the observation that in pregnancy, there is weight gain with increased body fat deposition[26,27]. The strong positive association between BMI and TSH may implicitly indicate the modifying influence of TSH. Our study showed that levels of TSH and thyroid hormones FT3 and FT4, were altered in apparently healthy Ghanaian women with normal pregnancies when compared to non-pregnant women. We found that TSH levels were significantly lower in pregnant women when compared to their non-pregnant counterparts, whereas FT3 was significantly higher in pregnant women. FT4 levels did not show any significant difference between the two study groups, although it was lower in pregnant women. Our observation is consistent that of others[28,29] who found the mean TSH throughout the three trimesters to be significantly lower in a case-control study. The proposed mechanism for the elevation in FT3 levels has to do with an increase in the activity placental deiodinase, which converts T4 to reverse T3 and FT3[30]. In the absence of overt thyroid disease, some controversy remains over FT3 and FT4 levels during pregnancy. Other have reported an increase in mean TSH levels during pregnancy[11]. The disparity in these outcomes on TSH levels could be due to differences in sample size, local populations sampled, or the iodine-sufficiency of the study populations. As observed by Roos *et al.*[13], our analysis showed a positive correlation between TSH levels and TG levels in pregnant women. Similar correlations have also been also reported [31,32]. However, Suhad and Salman reported a non-significant negative correlation between TSH and TG[33]. These deviating correlations may be due to additional factors that also modulate the pituitary-thyroid axis during pregnancy such as immune changes that occur during pregnancy[34], or the different assays used during this physiologic state. Our results illustrate the well documented relationship between increasing TSH levels throughout gestation[35]. Varying TSH with gestational age highlights the fact that gestational-age dependent reference ranges for FT3, FT4 would be more useful in making better interpretation of thyroid hormone status for a local population. Previous studies have shown that TSH, FT4 and FT3 are significantly

associated with lipid profile in the euthyroid population, regardless of gender[14]. The influence of TSH on lipid profile has been assumed to be mediated indirectly, through its effect on thyroid hormones. Furthermore, additional evidence indicates that this association is partially contributed by the direct extra-thyroidal effect of TSH on lipid profile[16]. However, non-significant positive association between TC and TSH, TG and TSH observed among pregnant women may support the assumption that TSH directly affects lipid metabolism[15]. Circulatory FT3 levels are inversely influenced by TSH, consequently the negative relationship with TG among pregnant women could also be attributed to low TSH level and the stimulation of lipid metabolism by FT3. Hyperthyroidism is implicated in hepatic endogenous glucose efflux which triggers lipogenesis [36,37]. TSH level was found to be associated with gestational age in this study. This may be a physiological role of TSH to maintain FT3 level to regulate TG synthesis with respect to gestational age. A study showed that high lipid parameters during pregnancy poses no immediate cardiovascular threat[38].

CONCLUSION:

Our results are in agreement with the general consensus that there are changes in levels of TSH and thyroid hormones during pregnancy, albeit within the normal reference range. However, there is the need for gestational-age dependent reference ranges for FT3, FT4 in the Ghanaian population to adequately assess thyroidal effects of TSH on lipid profile.

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CONFLICT OF INTEREST:

All authors declare that there is no conflict of interest, be it financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence this study.

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