Association between Thyroid Status and Lipid Levels among Pregnant Women in Jaffna District

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Abstract— *Thyroid dysfunction during pregnancy is associated with various adverse perinatal and maternal outcomes. Evidence shows that thyroid-stimulating hormone (TSH) may exert extra-thyroidal effects and modify the serum lipid levels. The aim of the study was to assess the thyroid status and its association with serum lipid levels among pregnant women during the third trimester of gestation. Among 477 pregnant women, serum thyroid stimulating hormone (TSH) and free thyroxine (fT_4) were assayed and also total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein (LDL-C) were measured and analyzed. Statistical analysis was done using SPSS. Mean age, weight, height and gestational age of the study subjects were 28.95(±5.46) years, 63.02 (±11.56) kg, 154.39 (±6.00) cm and 39.33(±1.37) weeks respectively. Median values of the serum TSH and free T_4 were 1.9 mIU/L and 12.6 pmol/L respectively. Also, serum TSH level ranged from 0.2 to 16.4 mIU/L whereas serum free T_4 level ranged from 10.1 to 28.2 pmol/L. Further, inter-quartile range (IQR) of TSH and free T_4 were 1.2 mIU/L and 2.7 pmol/L respectively. Among the study subjects, maternal serum TSH and serum free T_4 were not significantly correlated with serum lipid level (TC, TG, LDL-C and HDL-C). Serum TSH among maternal hypothyroid women were positively significantly correlated with serum TC (r=0.649, p=0.004) and LDL-C (r=0.745, p=0.001) and was not significantly correlated with TG (r=0.532, p=0.158) and HDL-C (r=0.327, p=0.186). Further, no correlation was obtained between serum free T_4 and serum lipid levels among maternal hypothyroid women. These results indicated that among the study subjects, maternal serum TSH and serum free T_4 were not significantly correlated with serum lipid level and significantly elevated serum lipid levels occurred in hypothyroid subjects. However, there is a need for gestational-age dependent reference ranges for TSH and free T_4 as well as lipid profile among Jaffna population to adequately assess thyroidal effects.*

Keywords: *Pregnant Women, Lipid Level, Thyroid Profile*

I. INTRODUCTION

Pregnancy is a state of significant dynamic changes in metabolism, with accumulation of lipids and nutrients during the first half; whereas during late pregnancy and lactation, these accumulated reserves are used for fetal growth and subsequently for milk synthesis (Hapon, et al., 2003). The regulation and coordination of lipid metabolism in pregnancy is very important because of the sudden and profound physiological changes occurring during these states (Hapon, et al., 2005). It is known that undiagnosed hypothyroidism during pregnancy will lead to irreparable central nervous system defects in the newborn because the development of the child in utero is critically affected by the mother's thyroid status (Gartner, 2009). The patients with subclinical hypothyroidism (TSH > 4.8 mIU/L) have higher serum TG levels and lower serum HDL-C levels than euthyroid subjects (Lai, et al., 2011) and its prevalence among women of childbearing ages is 4-5% (Glinoer, 1997). Further, cholesterol is an essential constituent of most biological membranes and is also a precursor of bile acids, steroid hormones, and certain vitamins. The liver is central in cholesterol metabolism, balancing hepatic cholesterol synthesis and hepatic uptake of plasma lipoproteins from the circulation against the excretion of hepatic cholesterol and bile acids in the bile. Thyroid hormone is an important regulator of cholesterol metabolism and T_3 can influence the metabolism of cholesterol at several critical steps in the liver: 1- the low-density lipoprotein receptor (LDL-R), which mediates cholesterol uptake from the circulation, 2,3-hydroxy-3-methylglutaryl coenzyme-A reductase, controlling cholesterol biosynthesis, and 3-cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in the synthesis of bile acids where cholesterol is used as substrate (Gullberg, *et al.*, 2002). When sterols accumulate, the 2-3-hydroxy-3-methylglutaryl coenzyme A reductase is rapidly degraded, resulting in the

termination of sterol synthesis (Eberlé, *et al.*, 2004; Dong & Tang, 2010).

Reduced binding activity of hepatic LDL receptors is generally considered as a major mechanism of hyperlipidemia in hypothyroidism and clearly effects of T3 on LDL receptor mRNA, but they could not be distinctly ascribed to TRα1 or TRβ. Further, T_3 rapidly regulates the transcription of the LDL receptor gene; no specific TRE (thyroid response element) has so far been described in the lDL receptor gene promoter. The suppression of CYP7A activity would lead to down-regulation of LDL receptor mRNA, however, it cannot be concluded that T_3 directly regulates the LDL receptor transcription (Lopez, et al., 2007).

Worldwide, limited studies have been conducted among pregnant women on serum lipid profile and its association with serum thyroid status. Further, no such type of published data is available especially in war affected regions of Jaffna District in Sri Lanka. Therefore, this study was carried out to provide information regarding the serum lipid status and the impact of thyroid profile on lipid level in pregnant women in Jaffna district at the third trimester of gestation.

II. MATERIALS AND METHODS

A. Experimental design

The study population consisted of randomly selected 477 pregnant mothers at third trimester of gestation in six selected Medical Offices of Health (MOH) Divisions (Jaffna, Uduvil, Nallur, Kopay, Karaveddy and Kayts) out of 12 MOH in Jaffna District. Once enrolled, all the subjects were advised to attend their antenatal clinic at 0800 hours in the morning with 12 or 14 hours overnight fasting. A fasting sample of 5 mL of venous blood was drawn before taking any oral drugs. Blood sample was centrifuged at 5000 rpm for 10 minutes and serum was separated and stored in acid washed polystyrene tubes at -80°C until the analysis for serum lipid profile was carried out at the Department of Biochemistry, Faculty of Medicine, University of Jaffna. Remaining portion of the serum was stored in other aliquots at -80°C until transported to the Nuclear Medicine Unit, Faculty of Medicine, University of Ruhuna for analysis of serum *thyroid stimulating hormone (*TSH) and free thyroxine (fT_4). Maternal serum TSH and free T_4 were measured among 477 women using Enzyme-Linked Immuno Sorbant Assay (ELISA) technique and serum lipids (TC, HDL-C, LDL-C and TG) were measured using fully automatic biochemical analyzer (ERBA XL-200, Germany). Further, systolic (SBP) and diastolic (DBP) blood pressures (5 minutes seated rest, mean of two readings) were recorded at baseline using a sphygmomanometer.

B. Statistical Analysis

The results were presented as mean, standard deviation, median, inter-quartile range (IQR) or observed range. Simple linear regression analysis was used to test for correlations between these variables. A p value less than 0.05 were considered as significant. All data processing was conducted using the SPSS Version 16.0 software for Windows.

C. Ethical considerations

Ethical clearance was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Jaffna, Jaffna, Sri Lanka. Permission was obtained from the Director, Teaching Hospital and Regional Director of Health Services (RDHS), Jaffna, Sri Lanka and Consultants of the Obstetric wards in relevant hospitals in Jaffna District to recruit mothers for the study.

III. RESULTS

A. Baseline characteristics of the women

Among the 500 pregnant women, who were recruited for the study, 20 of them were excluded because of missing data or being lost during the study period (e.g., shifted their residence before delivery of the baby and baby delivered elsewhere in Jaffna) and three newborns died immediately after the delivery. Therefore finally, the investigator included 477 pregnant women in the sample. Of the 477 pregnant women, 98% (n=467) delivered their babies at one of the government hospitals in Jaffna district and only 2% (n=10) had chosen a private hospital. All the subjects have followed their antenatal clinic regularly for routine medical checkup. The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 105.53 (±10.30) and 69.40 (±7.05) mm Hg respectively. Pregnant mothers were considered hypertensive if SBP was ≥140 mm Hg or DBP was ≥ 90 mm Hg and only 1.0 % (n=5) of them had gestational hypertension. According to the neck examination which was carried out among these women by inspection and palpation for goiter, 3% (n=15) of them had goiter. From the questionnaire, 4% (n=19) of the pregnant women reported to suffer from asthma. Of the study subjects, 18 women had gestational diabetes and only two women reported to be vegetarians throughout the gestation.

B. Socio-demographic characteristics

Other baseline characteristics of the study subjects are given in Table1. Maternal age was categorized as <20, 20-29, 30-39 and ≥ 40 years. Of them 52% (n=248) were 20-29 years, while 44% (n=210) of subjects were belonging to 30-39 years of age. Thirty two percent (n=152) of the

mothers were found to be in the height range between 150.0-154.9 cm and 28 % (*n*=136) of them between 155.0- 159.9 cm. More than one third of mothers (35.0 %; *n*=169) were in the weight range of 51.0-60.0 kg and 29.0 % (*n*=138) of them were on 61.0-70.0 kg. The educational attainment of participants was categorized as non formal (0.2; *n*=1), grade 1-5 (9.6; *n*=46), grades 6-11(58.9; *n*=281), Grade 12-13 (23.9; *n*=114) and degree or above (7.3%; n=35) respectively.

Only 9.3 % (*n*=46) of mothers were employed in the government sector. Among the mothers 58.9 % (*n*=281) studied up to ordinary level (GCE O/L), 23.9 % (*n*=114) studied up to advanced level (GCE A/L) whereas only 7.3 % (*n*=35) completed their higher degree while one mother was identified as illiterate. Respondents were divided into four income groups according to their household income in Sri Lankan Rupees. Majority of the mothers [67.3 % (n=321)] had the average monthly household income of SLR 20000 or above (Table 1).

C. Maternal serum TSH and fT_4

Reference range of maternal serum TSH concentration is 0.2- 5.2 mIU/L and maternal hypothyroidism is defined as serum TSH >5.2 mIU/L (Pesce, 2007). Among the 477 of pregnant mothers, only 3.4 %; *n*=16 were hypothyroid. Reference range of maternal serum free T_4 is 6.4 - 25.7 pmol/L (Pesce, 2007). Median values of the serum TSH and free T_4 were 1.9 mIU/L and 12.6 pmol/L respectively. The serum TSH level ranged from 0.20 to 16.40 mIU/L whereas serum fT_4 level ranged from 10.1 to 28.2 pmol/L.

D. Maternal serum lipid levels

Among the 477 mothers, mean values of serum TC (range 55.0 - 477.0 mg/dL), LDL-C (range 72.0 - 342.7 mg/dL), HDL-C (range 23.1 - 165.6 mg/dL) and TG (range 90.0 - 594.0 mg/dL) were 262.4 ± 52.8, 168.9 ± 42.9, 77.0 ± 21.2 and 273.1 ± 97.2 mg/dL respectively. Normal ranges of serum LDL-C, HDL-C, TG and TC for non-pregnant women were <100 mg/dL, 42.0 - 88.0 mg/dL, 35.0 - 135.0 mg/dL and <200 mg/dL respectively (Esther & Duncan, 2004). In my study, normal range of serum TC, TG, LDL-C and HDL-C level were obtained among pregnant mothers 9.6 % (*n*=48), 4.6 % (*n*=23), 3.4 % (*n*=17) and 70.6 % (*n*=353) respectively.

Among the total 477 mothers, serum TSH and serum fT_4 were not correlated with serum lipid profile level (TC, TG, LDL-C and HDL-C). However, maternal serum TSH among hypothyroid mothers were positively significantly correlated with serum TC (r=0.649, p=0.004) and LDL-C (r=0.745, p=0.001). Further, serum TSH was not significantly correlated with TG (r=0.532, p=0.158) and HDL-C (r=0.327, p=0.186) at third trimester of gestation (Table 2). No correlation was observed between serum fT_4 among hypothyroid mothers and lipid status.

Table 1: Baseline characteristics of the pregnant mothers

Socio-demographic Characteristics	Number (%)
Age (years)	
<20	7 (1.5)
20-29.9	248 (52.0)
30-39.9	210 (44.0)
≥40	12 (2.5)
Height (cm)	
<144.9	23 (4.8)
145-149.9	69 (14.4)
150-154.9	152 (31.9)
155-159.9	136 (28.5)
160-164.9	97 (20.4)
Weight (kg)	
Upto 50	64 (13.4)
50.1-60	169 (35.4)
60.1-70	138 (28.9)
Above 70	106 (22.3)
Educational attainment	
Non formal	1 (0.2)
Gr. 1-5	46 (9.6)
Gr. 6-11	281 (58.9)
Gr. 12 and 13	114 (23.9)
Degree or above	35 (7.3)
Gestational age (weeks)	
Pre term (<37 weeks)	12 (2.5)
Term (37-41 weeks)	453 (95)
Post term (≥42 weeks)	12 (2.5)
Household income	
0-9,999	24 (5.0)
10,000-19,999	132 (27.7)
20,000-29,999	178 (37.3)
≥30,000	143 (30.0)
Employability	
Govt./Private Sector	46 (9.3)
House wives	431 (90.7)

E. Association of maternal thyroid profile (TSH and fT_4) with lipid status

Table 2: Correlation of serum TSH and fT_4 level with lipids levels among hypothyroid mothers

Maternal Parameters		r value	p value
TSH	TC	0.649	0.004*
TSH	TG	0.532	0.158
TSH	LDL-C	0.745	0.001*
TSH	HDL-C	0.327	0.186
fT_4	TC	0.264	0.346
fT_4	TG	0.079	0.772
fT_4	LDL-C	0.346	0.189
fT_4	HDL-C	0.168	0.555

*A two-sided *p*-value of <0.05 was considered as statistical significance

Period of gestation at delivery of a child was categorized as preterm (<37 weeks), term (37-41 weeks) and post term (≥42 weeks). In this study, period of gestation at delivery was categorized from 37 to 42 weeks for 95.0 % (*n*=453) of pregnant mothers and 2.5 % (*n*=12) of mothers delivered at <37 weeks and another 2.5% at ≥42 weeks. Among the pregnant mothers, most of them (95.0 %) delivered the baby during term (Table 1). Further, data shows that there was a positive significant correlation obtained between gestational period of mother at the time of delivery and serum TC (r =0.091, p = 0.047), TG (r = 0.092, p =0.045) and LDL-C (r =0.094, p = 0.041). But, there was no positive significant correlation observed between gestational period and serum HDL-C (r =0.012, p>0.05).

IV. DISCUSSION

A. Iodine status in pregnancy

Iodine deficiency is one of the major WHO nutritional priorities in global health (ICCIDD, 2007). It is estimated to cause a global loss of 13.5 IQ points at population level (Bleichrodt & Born, 1994), constituting the world's greatest single cause of preventable brain damage and mental retardation (Delange, *et al.,* 2001a). Iodine deficiency is still the most widespread cause of maternal hypothyroxinemia in developing countries including Sri Lanka. Detection at birth, by blood spot TSH estimation among newborn is unlikely to identify mild iodine deficiency and would fail to identify those exposed to a period of iodine deficiency earlier in pregnancy, at a time probably too late for the treatment to normalize the development (Bahn, *et al.,* 2011). Therefore, it is possible that many minor learning disabilities may be preventable by advising women through antenatal clinics to take iodine supplements or correct usage of iodized salts as soon as possible in early pregnancy, or before (Delange, *et al.,* 2001b).

B. Lipid status during gestation

A growing body of evidence consistent in several animal and human studies suggests adverse consequences of maternal hypercholesterolemia (Catov, *et al.,* 2007; Gonzalez-Clemente, *et al,* 2007; Palinski, *et al.,* 2001; Goharkhay, *et al.,* 2008; Bartels & O'Donoghue, 2011). This present study indicates that majority of the pregnant mothers during third trimester had elevated serum lipid levels than the reference level of non-pregnant counter parts. Further, it has been found that with increased gestational age, the tendency of serum lipids elevation was more obvious in late pregnancy and serum TG, TC and LDL-C levels significantly increased, which was consistent with the other relevant published studies (Lippi, *et al.,* 2007; Husain, *et al.,* 2008; Bartels & O'Donoghue, 2011; Dos, *et al.,* 2013). A study conducted in India among mothers revealed that the serum lipid was increased appreciably during the pregnancy (Mankuta, *et al.,* 2010). Furthermore, a study reported that during normal pregnancy all lipid components increased in parallel to the increase in gestational age and this increase was reported to be secondary to the increase in estrogen and progesterone levels during gestation (Mankuta, *et al.,* 2010; Vrijkotte, *et al.,* 2012). Another study conducted in Italy indicated that a significant increase in serum TC with gestational period at delivery (Tranquilli, *et al,* 2003). Study in Nigeria revealed that serum TC level was significantly high during the gestation when compared with that of the non-pregnant counter parts (Okojie & Blessing, 2011). This present study found that higher values for serum TC, TG and LDL-C during late pregnancy and specific reference values for lipid levels in pregnancy have been established and there by extreme maternal hypercholesterolemia could be recognized and monitored.

A recent study shows that patients with subclinical hypothyroidism (TSH > 4.8mIU/L) have higher serum triglyceride levels and lower serum HDL-C levels than euthyroid subjects (Lai, *et al.,* 2011). Furthermore, a study revealed that noticeable reduction in serum TC with inversely correlated to free T_4 levels, but not correlated with serum TSH levels (Tagami, *et al.,* 2010). In contrast, a population-based study conducted among 1350 subjects both female and male with subclinical hypothyroidism showed no change in mean levels of serum TC, TG and LDL-C (Lu, *et al.,* 2011). However, this present study found that the mean serum TSH levels were higher in subjects with hypothyroidism, indicating a significant positive relationship between serum TSH-TC, and TSH-LDL-C levels. However, further properly

controlled prospective studies with a larger sample sizes are necessary to find out the relationship between these parameters.

CONCLUSION

Present data indicated that a positive significant correlation of serum TSH of hypothyroid mothers with TC (r=0.649, p=0.004) and LDL-C (r=0.745, p=0.001) in this study area. Further, mothers identified with high serum lipid levels during pregnancy may need follow-up postnatally as persistent hypercholesterolemia substantially increases the risk of atherosclerosis.

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