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A Study of Association between Lipid Profile and Thyroid Hormones in Pregnancy

Dr. Rajkumari Vidyabati Devi[1], Dr Sujeeta Oinam[2], Dr. R.K. Bishwalata[3], Dr. Ng. Indrakumar Singh[4], Prof T. Rajen Singh[5].

[1](Department of Biochemistry, Jawaharlal Nehru Institute of Medical Sciences, India, Associate Professor)
[2](Department of Biochemistry, Jawaharlal Nehru Institute of Medical Sciences, India, Senior Resident)
[3](Department of Community Medicine, Jawaharlal Nehru Institute of Medical Sciences, India, Associate Professor)
[4](Department of Obstetrics and Gynaecology, Jawaharlal Nehru Institute of Medical Sciences, India, Professor)
[5](Department of Biochemistry, Jawaharlal Nehru Institute of Medical Sciences, India, Professor)
Corresponding Author: Dr. Rajkumari Vidyabati Devi

Abstract
Background: *To study the association between lipid profile and thyroid hormones in early pregnancy* ***Aims:****To investigate lipid profiles and thyroid hormones, US -TSH , FT_4, FT_3 during early pregnancy. To find out the association between thyroid dysfunction and serum lipid levels during early pregnancy.* ***Materials and methods****: This prospective observational study was conducted at the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Jawaharlal Nehru Institute of Medical Sciences, Imphal during the period of July 2015 to January 2016. A total of four hundred and ninety seven pregnant women within the first twelve weeks of gestation were the study subject. Patients documented with history of hypothyroidism, thyrotoxicosis, Hypertenship pregnant women patients suffering from other medical problems , under treatments were excluded. Estimation of lipid profile were done by enzymatic colorimetric test. Estimation of ultrasensitive TSH (U-TSH) ELISA, free T_3 Micro well ELISA, Free T_4 Micro well ELISA – Enzyme immune assay – qualitative determination of Free T_3, T_4 hormone concentration of human serum were done.* ***Results:****The mean of thyroid parameters free T_3, Free T_4 Sensitive, (U-TSH) Elisa were, 27,71 (6.170)ng/ml, 1.82 (2.46)ng/dl, 2.93 (4.21)µIU/mL respectively. Lipid profile parameters, total cholesterol and triglyceride 209.9 (28.67)mg/dL and 189.9 (36.85)mg/dl respectively. The total cholesterol, triglyceride and VLDL values are elevated among the subclinically hypothyroid pregnant women, when compared to healthy pregnant women.It has been observed that positive correlation is seen between TSH and Triglycerides which is statistically significant (p-value 0.000). The significant correlation was also seen with cholesterol and with LDL in subclinical Hypothyroid pregnant women.****Conclusion:*** *Correlation of Lipid and Thyroid profile, Screening for Dislipidemia and Thyroid Dysfuntion in Early Pregnancy is essential to prevent Maternal and foetal pregnancy complications and outcome.*

Keywords: *Subclinical hypothyroid, thyroid stimulating hormone, free thyroxine, Euthyroid, Dyslipidemia, Triglycerides, Total cholesterol.*

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I. Introduction

The thyroid gland is important in the human body because of its ability to produce the hormone triiodothyronine (T_3) and tetraiodothyromine (T_4), necessaries for appropriate energy level and active life. Thyroid hormones exert powerful and regulatory influences on growth, differentiation, cellular metabolism and general hormonal balance of the body, as well as on the maintenance of metabolic activity and the development of skeletal and organ system. Thyroxine hormone is secreted in the thyroid gland which is the most important componenent of the endocrine system. Over 99% thyroxine secreted in the blood is bound to thyroxine binding globulin (TBG), albumin and prealbumin. Approximately 0.3% T_4 is in the free unbound state in the blood. It is this small fraction that is generally recognized as the physiologically active fraction due to its ability to enter target cells. Once in the cells, % T_4 influence calorigenesis and protein, lipid and carbohydrate metabolism. T_4 also functions in the peripheral tissues as a prohormone by being further metabolized to another most active thyroid hormone, tri-iodothyromine (T_3) and other inactive metabolites reverse T_3. Expected ranges of FT_3 in pregnancy is 0.76 – 2.24 (mg/dL).

It has long been known that thyroid hormones are vital importance in maintaining the initial level of phospholipids in cell membranes and fatty acids composition of Lipids. (1) T_3 plays a critical role in lipid metabolism by regulating genes involved in lipogenesis and lypolypis.(2)The determination of serum levels of thyroid stimulating hormone is recognized as an important measurement in the assessment of thyroid function. Thyroid stimulating hormone is secreted by the antrerior lobe of the pituitary gland and induces the production and release of thyroxine(T4) and triiodothronine(T3) from the thyroid gland. (4)

Hypothyroidism, characterized by low serum thyroid hormone levels, in association with reduced metabolism, reduced lipolysis, weight gain, reduced cholesterol. Thyroid hormones exert their effects by stimulation of thyroid hormone receptors (TRs) that have different tissue distribution and metabolic targets.(3) Abnormal serum thyrotropin (TSH) values and thyroid dysfunction are more prevalent in women than men and increase with age.(5) Subclinical thyroid dysfunction may be defined as an elevated TSH concentration in an asymptomatic patient with a normal serum free thyroxine concentration.(6) Subclinical hypothyroidism (SCH) is the commonest form of hypothyroidism in pregnancy with an estimated the prevalence of 2.5% identified through routine screening.(7)

In our country, prevalence of SCH varies from 2.8% in South India to 14.3% in the northern part of the country.(8,9). During pregnancy, hormonal changes and increased metabolic demands lead to profound alterations in the biochemical parameters of thyroid function and lipid profile, resulting an increase in thyroid hormone synthesis(11) and total cholesterol.(12) Maternal thyroid hormones and cholesterol plays a vital role in the development and function of both the fetus and the placenta.(13)

Maternal hypothyroidism in the first trimester of 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 mothers thyroid status.(14) Plasma lipid profiles in the first trimester of pregnancy may predict the incidence and severity of preeclampsia. The objective of this study is to investigation prevalence of thyroid dysfunction, the impact of hypothyroidism on lipid profile during early pregnancy.

II. Materials And Methods

This prospective observational study was conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Jawaharlal Nehru Institute of Medical Sciences, Imphal during the period of July 2015 to January 2016. The Ethical Committee of Jawaharlal Nehru Institute of Medical Sciences, Imphal approved the study protocol. The objectives of the study were explained and written consent was taken from individual subjects. A total of four hundred ninety seven pregnant women living in iodine adequate areas within the first twelve weeks of gestation were the study subjects. Duration of gestation were evaluated on the dates of their last menstrual period confirmed by ultrasonography.

Exclusion criteria:

All cases of previous history of essential hypertension or chronic hypertension, known cases of thyroid disorders and associated molar pregnancy and multiple pregnancies were excluded from the study.

Specimen collection:

Blood samples were collected from antenatal clinic,OPD setting between 0900 and 1400 hours. Under all aseptic conditions, 5 ml blood sample was collected by venipuncture and allow to clot. The serum was then separated by ultracentrifugation of the sample at room temperature and serum was taken in a separate test tube. The serum was then used for thyroid and lipid profile analysis in laboratory.

III. Methodology

Thyroid profile was done by Micro well ELISA, Free T_4 Micro well ELISA – Enzyme immune assay – quantitative determination – free T_3, T_4 hormone concentration – human serum, using kits from Benesphere TM. Ultra sensitive TSH (U-TSH) ELISA – done by quantitative determination of thyroid stimulating hormone TSH concentration in serum using kits from DRG ultra – sensitive TSH (U-TSH) ELISA (EIA – 1790) DRG International Inc. USA.

Estimation of lipid profile were done by enzymatic colorimetric test with lipid clearing factor (LCF) by using kits marketed by Human Gesellschaft fur Biochemica and DiagnosticambH Max-PLANCK-RING21 D65205 WIESBADEN, GERMANY through its Indian branch supply. LDL-Cholesterol; Calculated by Friedwald formula.

- The first trimester specific reference values for U-TSH 0.54-4.72 μIU/mL.
- FT_4 0.76-2.24 ng/dL
- Based on first trimester specific reference values euthyroid defined as

FT_4-TSH 0.76 – 2.24 ng/dL – 0.54-4.72 μIU/ml respectively

- All women having normal FT_4 with U-TSH > 4.72 μIU/ml – diagnosed – subclinical hypothyroid (SCH)

- The USA National Institute of Health's National Human Genome Research (NIH-NHR) came up
- Reference range – Total cholesterol levels – Pregnant women
- NIH-NHR proposed – Low serum cholesterol level < 4 mmol/litres – 154 mg/dL
- Moderate total cholesterol lies between 4 and 6.8 mmol/litre (154-263 mg)/dL
- High level above 6.8 mmol/litre> 263 mg/dL.
- First trimester reference intervals for Triglycerides – 40-159 mg/dL.
- Lipid profile parameters are correlated with the thyroid dysfunction during first trimester – Pregnancy

Statistical analysis:
The data were entered in excel sheet and analyzed using descriptive statistics means and standard deviation and various outcomes measured and calculated using SPSS Windows Version 22.

IV. Results

A total of fourhundred and ninetyseven pregnant women in early pregnancy having gestational period of twelve to fourteen weeks were studied. The average gestational period were twelve weeks (37.4%). Maximum number of the study subjects were (P_2+0) comprising (49.9%) of the study group. The average age of the study group range from 17-43 years, Mean (SD) 27.71 (6.170). The mean of thyroid parameters free T_3, Free T_4 Sensitive, (U-TSH) Elisa were, 27,71 (6.170)ng/ml, 1.82 (2.46)ng/dl, 2.93 (4.21)µIU/ml respectively. While the mean of lipid profile parameters, total cholesterol and triglyceride 209.9 (28.67)mg/dL and 189.9 (36.85)mg/dl, Respectively (Table 1). It has been observed, based on the first trimester-specific reference intervals among 497 pregnant women 422 (84.4%) were diagnosed as euthyroid, seventy five (15.1%) as subclinical hypothyroidism (SCH). (Table No. 6).

As per the early recognition of moderate rise of triglyceride, cholesterol during early pregnancy can predict pregnancy related complications. There is a high incidence of thyroid dysfunction during pregnancy resulting in adverse maternal (miscarriages, anemia in pregnancy, pre-eclampsia) and fetal effects (Premature birth), low birth weight, increased neonatal respiratory distress) which may justify for screening for thyroid function during pregnancy. Pregnancy is a physiological process to supply adequate nutrition to the growing fetus maternal physiological adjustment with different organ system occur during pregnancy. Studies reported the disturbance in the lipid metabolism in patients with patients with SCH(15). The Colorado Thyroid disease prevalence study (16) showed that TC and LDL-C in SCH were significantly higher than in euthyroidism which is in agreement with our present study.

It was observed that TSH, T_3, T_4 increased significantly among the pregnant women who were diagnosed as subclinical hypothyroidism.

The total cholesterol, triglyceride and VLDL values are elevated to those subclinically Hypothyroid pregnant women, when compared to healthy pregnant women. The T test between TSH level and Lipid profile among the normal healthy pregnant women (422) and pregnant women with subclinical Hypothyroid (75) are shown in Table No.6.

It has been observed that positive correlation is seen between TSH and Triglycerides which is statistically significant. The significant correlation was also seen with cholesterol and with LDL in subclinical Hypothyroid pregnant women.

V. Discussion

Maternal thyroid dysfunction during pregnancy has been shown to be associated with a number of adverse outcomes. Elevated maternal thyroid stimulating hormone (TSH) has been associated with an increased risk of pre-term birth, impaired neurological development in the child. Subclinical Thyroid dysfunction are more prevalent which are frequently remains undiagnosed unless specific screening programs – are initiated to diagnose thyroid function abnormalities during early gestation, if left untreated which will turn to overt hypothyroidism. Thyroid function tests change during pregnancy due to the influence of two main hormones: human chorionic gonadotropin (hCG), the hormone that is measured in the pregnancy test and estrogen, the main female hormone. (17) In addition, in pregnancy, the stimulatory effect of serum hCG of placental origin, increased metabolic demand, and mental stress may play increase overall thyroid activity and elevate thyroid hormone levels. During pregnancy, increased estrogen levels cause increased production of proteins by the liver. As a result, hypatocytes increases their production of thyroid binding globulin, the protein that tranaports T_4 in the circulation. High estrogen, on the other hand, due to oligosaccharide modification, reduces peripheral degradation of thyroid binding globulin. As a result, the content of thyroid binding globulin in the serum is increased.

Roose et al (18) demonstrated an association between serum TSH and higher TG. A recent study shows that patients with SCH (TSH>4.8mlU/L) have higher serum triglyceride levels and lower serum HDL-C levels than euthyroid subjects.(19) As per the American Thyroid Association (ATA) Guidelines and Recent Endocrine

Society guidelines (20) our study – used 0.54 – 4.72μIU/ml as the "reference" range foUS- TSH values in the first trimester of pregnancy.

In our study total cholesterol was mildly increased and triglyceride was moderately increased in both SCH and ethyroid pregnant women, which is statistically significant P-value (0.000). The American Association of clinical Endocrinologist (AACE) recommended thyroid function screening all pregnant women during the first trimester of pregnancy.(21) Hypertriglyceridemic have been attributed to the hormonal affects of progesterone-estrogen. Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides.

In the present study correlation was observed between all parameters of thyroid and lipid profile in preeclampsia patients. It has been observed that positive correlation is seen only between TSH and Triglycerides in subclinical hypothyroid pregnant women. The principle modulator of this hyper triglyceridemia is hyperoestrogenemia in pregnancy that induces hepatic biosynthesis of Triglycerides. Estrogens stimulate expression of TBG in liver and the normal rise in estrogen during pregnancy induces roughly a doubling in serum TBG concentrations. Increased levels of TBG lead to lowered free T3 and T4 concentrations, which results in elevated TSH secretion by the pituitary and, consequently, enhanced production and secretion of thyroid hormones.(22)

Serum TSHUS>4.72 μIU/L in pregnant women should be used as a guide for the severity, it is best to measure FT_4. The risk of progression to hypothyroidism could be predicted from serum TSH levels. The recent guidelines for diagnosing and managing thyroid disease during pregnancy issued by American Thyroid Association recommend – trimester specific reference intervals for TSH, as well as US- TSH targets for diagnosing and treating hypothyroidism during pregnancy. Elevated maternal thyroid stimulating hormone (TSH) has been associated with an increased risk of pre-term birth, placental abruption, foetal death, and impaired nuerological development in the child. Our study intended to correlate lipid profile and thyroid dysfunction in early pregnancy. It is well established that there is a big increase in concentration of thyroid binding globulin (TBG) during pregnancy due to influence of high levels of circulating estrogens .A recent study made in 1534 Chinese subjects shows that paitients with subclinical hypothyroidismUS- TSHabove 4.78 have higher serum triglycerides levels and lower HDL-C Levels than euthyroid subject20 , which is consistent with our study.

Many studies have been reported that altered lipid levels were due to abnormal lipoprotein metabolism which play an important role in pathogenesis of pregnancy induced hypertension. Endothelial dysfunction is the pathogenics of pre-eclampsia and lipids gave role on this event. Triglycerides and total cholesterol levels gradually increased from the first to third trimester. (21) Plasma lipid profile in the first trimester of pregnancy may predict the incidence and severity of pre-eclampsia. Early recognition of moderate rise of cholesterol and Triglycerides during early pregnancy can predict the pregnancy related complications. From the present study it is recommended that all pregnant women should be measured serum TSH, FT_4, FT_3 and lipid profile in the first trimester of their pregnancy.

VI. Conclusion

In the present study it is observed that, among the parameters of lipid profile, Triglycerides Total cholesterol and VLDL are increased significantly among the SCH pregnant women when compare with the Euthyroid pregnant women. There was significant positive correlation observed between US- TSH and Triglycerides when compare to normal euthyroid thyroid pregnant women. Early recognition of moderate rise of Triglyceride,total cholesterol, during early pregnancy can predict pregnancy related complications. In view of these associations with adverse outcomes,all pregnant women should be screened for thyroid dysfunction and lipid profile to identify those at at risk.

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Table 1: Thyroid profile and lipid profile in early pregnancy

Variable	Range	Mean (SD)
Age (yr)	17-43	27.71 (6.170)
T3	0.20-3.30	2.05 (1.99)
T4	0.30-30.0	1.82 (2.46)
TSH	0.10-50.0	2.93 (4.21)
TC	146.2-309.0	209.9 (28.670)
TG	114.28-333.3	189.9 (36.85)
HDL	32.94 – 80.0	48.8 (9.95)
VLDL	22.86-66.6	38.1 97.52)
LDL	71.16-193.0	122.4(22.65)

Table – 2: Showing Parity of the Pregnant women

Variable	**Frequency**	**%**
P0+0	125	25.2
P1+0	124	24.9
P2+0	248	49.9
Total	**497**	

Table – 3 : Weeks of Pregnancy

Weeks	**Number**	**%**
10	186	37.4
12	187	37.6
14	124	14.9
Total	497	

Table – 4: Showing T_4 Profile 377 of the pregnant women had T_4 level 0.76 to 2.24 (75.9%), Seventy Pregnant women had T_4 level 0.76 to 2.24 (75.9%), Seventy Pregnant Women had T_4 level <2.24(14.1%), Fifty Pregnant of T_4 level <0.76(10.1%)

T4 Level	Number	%
<0.76	50	10.1
0.76 to 2.24	377	75.9
<2.24	70	14.1
Total	497	

Table 5: Showing TSH Profile

TSH Level	Number	%
<4.7	422	84.9
4.7 & above	75	15.1
<2.24	70	14.1
Total	497	

Table 6: Showing T test between TSH Level and Lipid Profile

Lipid profile Mean (SD)	TSH		Mean difference	T-value	P-value
	Normal (422)	Hypo (75)			
TC	206.4 (26.3)	229.8 (33.1)	-23.37	-6.794	0.000
TG	186.5 (33.2)	209.5 (48.7)	-23.01	-5.108	0.000
HDL	49.1 (10.01)	47.8 (9.6)	1.267	1.016	01.310
VLDL	37.4 (6.8)	41.9 (9.7)	-4.479	-4.857	0.000
LDL	119.4 (20.9)	138.9 (24.9)	-19.516	-7.221	0.000

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