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Research Article

ASSOCIATION BETWEEN THYROID AUTOIMMUNITY AND SERUM LIPID LEVELS DURING EARLY PREGNANCY

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ABSTRACT

Objective: The aim of this study is to find out the prevalence of thyroid autoimmunity during the first trimester of pregnancy and correlated with serum lipid parameters. **Materials and Methods:** This study, conducted on 233 pregnant women of age between 18 and 35 years during the first trimester. Serum thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroperoxidase antibodies (TPO-Ab), total cholesterol and triglycerides were analyzed. The significance of prevalence and relative risk of thyroid autoimmunity was calculated by using medcalc easy to use statistical software bvba, version 16.4.3, Ostend. A p-value of ≤ 0.05 was taken as statistically significant. **Results:** The overall prevalence of autoimmunity was 12.4% with the mean of 198.2 IU/ml. The prevalence of subclinical hypothyroid was 30.9%; among them, 25% were thyroid autoantibody-positive pregnant women. The relative risk of autoimmunity was 3.66 times more in subclinical hypothyroid than euthyroid. The mean of TPO-Ab positive was significantly more in subclinical hypothyroid than euthyroid pregnant women with P=0.0003. The mean serum TSH values were significantly higher in TPO-Ab positive than TPO-Ab negative women with P=0.01. The prevalence of autoimmunity was more with TSH>2.5 µIU/L and with moderate levels of cholesterol (154 – 263 mg/dl). Conclusion: Subclinical hypothyroid is more prevalent and frequently remains undiagnosed during early pregnancy. The relative risk of thyroid autoimmunity was increased positively with TSH >2.5 µIU/L and with moderate levels of cholesterol. Thus, all the pregnant women must be screened for TPO-Ab titers, TSH, FT4 and total cholesterol during early pregnancy to predict high- risk pregnancy during early gestation.

INTRODUCTION

Thyroid disease is a common endocrine condition in women of reproductive age [1]. Subclinical hypothyroidism (SCH) is the commonest form of hypothyroidism in pregnancy with an estimated the prevalence of 2-5 % identified through routine screening [2]. In our country, prevalence of SCH varies from 2.8% in south India to 14.3% in the northern part of the country [3, 4]. The most common cause of hypothyroidism in women of reproductive age, in the absence of iodine deficiency, is an auto immune thyroid disorder (AITD) with a prevalence of 5–15%, but is not necessarily accompanied by thyroid dysfunction [5].

During pregnancy, hormonal changes, and increased metabolic demands lead to profound alterations in the biochemical parameters of thyroid function and lipid profile, resulting in an increase in thyroid hormone synthesis [6] and total cholesterol [7]. Maternal thyroid hormones and cholesterol plays a vital role in the development and function of both the fetus and the placenta [8]. Thyroid dysfunction can lead to spontaneous miscarriage, gestational hypertension, placental abruption, and premature delivery [9, 10]. Similarly, the presence of antibodies to thyroid peroxidase (TPO-Ab) has been associated with increased risk of miscarriage, preterm birth, failure to conceive with in vitro fertilization [11], and maternal postpartum thyroiditis [12]. Maternal hypothyroidism in the first trimester of pregnancy may be harmful to fetal brain development and lead to mental retardation [9]. Plasma lipid profiles in the first trimester of pregnancy may predict the incidence and severity of pre-eclampsia. In view of these associations with adverse outcomes, all pregnant women should be screened for thyroid dysfunction and lipid profile to identify those at risk.

The aim of this study is to find out the prevalence of thyroid dysfunction and thyroid autoimmunity during the first trimester of pregnancy and correlated with lipid abnormalities.

MATERIALS AND METHODS:

This study was conducted on 233 pregnant women of age between 18 and 35 years during the first trimester, attended in antenatal OP from January to June 2016 at the Government Maternity Hospital, Hyderabad, India. Two women had hyperthyroidism were excluded from the study. The study approved by the institutional ethical committee of Osmania Medical College, Hyderabad and informed consent was obtained from all pregnant women. Pregnant women with known thyroid problems and taking medications other than nutritional supplements, TSH>10 µIU/L, subclinical hyperthyroidism, DM, hypertension, and any other systemic disorder was excluded from the study. History was taken in detail including the present, past, obstetric, family, and personal history.

At least 5 ml of blood was obtained from all the selected pregnant women in the morning after an overnight fast after an informed consent was obtained. Serum was tested for thyroid stimulating hormone (TSH), free thyroxine (FT4), thyroperoxidase antibodies (TPO Ab), using a chemiluminescence immune assay, Thyrocare Technologies Ltd, India with commercially available kits by Novateinbio, USA. Total cholesterol and triglycerides were estimated by using a Transsessie semi autoanalyzer with commercially available ERBA kits. The first trimester-specific reference values for TSH 0.1-2.5µIU/l and for FT4 0.8-1.8 ng/dl were used to diagnose thyroid disorders. Based on first trimester-specific reference values euthyroid defined as FT4 and TSH are 0.8-1.8 ng/dl and 0.1-2.5 µIU/ml, respectively [13]. All the women having normal FT4 with TSH >2.5 µIU/ml were diagnosed as subclinical hypothyroid (SCH). The USA National Institute of Health's National Human Genome Research (NIH-NHR) came up with reference ranges of total cholesterol levels for pregnant women. NIH-NHR proposed that a low serum total cholesterol level lies below 4 mmol/liter (154 mg/dl), moderate total cholesterol lies between 4 and 6.8 mmol/liter (154 – 263 mg/dl) and high level is above 6.8 mmol/liter (>263 mg/dl) [14]. The first-trimester reference intervals for triglycerides are 40 – 159 mg /dl. These parameters were correlated with thyroid dysfunction during the first trimester of pregnancy.

Statistical analysis

Statistical analysis is carried out using Sofa Stats software (Open source statistics, analysis, and reporting software from Paton-Simpson & Associates Ltd.). Results were presented as mean, standard deviation (SD) for continuous variables; the frequency and percentage were given for qualitative variables. P value and 95% confidence interval between two different groups, relative risk, the 95% confidence interval of relative risk and the significance of a difference between two independent proportions were calculated by using medcalc easy to use statistical software bvba, version 16.4.3, Ostend. A p-value of ≤ 0.05 was taken as statistically significant.

RESULTS

The average age of 233 pregnant women enrolled in the study was 22.1 years. The mean of thyroid parameters; TPO-Ab, TSH, and FT4 were 35.95 IU/ml, 2.42 µIU/ml, and 1.18 ng/dl respectively, while the mean of lipid parameters; total cholesterol and triglycerides were 202.25 mg/dl and 161.97 mg/dl, respectively (Table 1).

Out of 233 pregnant women, 29 (12.4%) were positive for TPO-Ab, whereas 204 (87.6%) were negative for TPO-Ab. The mean of TPO –Ab positive was a significantly more than TPO-Ab negative (198.2 vs. 12.9 IU/ml, P< 0.0001). Based on the first trimester-specific reference intervals, among 233 pregnant women, 161 (69.1%) were diagnosed as euthyroid, 72 (30.9%) were diagnosed as SCH. Among 161 euthyroid women, 11 (6.8%) were TPO-Ab positive and 150 (93.2%) were TPO-Ab negative. There was a significant rise of the mean of TPO-Ab positive than TPO-Ab negative (133.3 vs. 13.1 IU/ml, P<0.0001) in euthyroid pregnant women. Among 72 SCH, 18 (25%) were TPO-Ab positive, 54 (75%) were TPO-Ab negative. There was a significant rise of the mean of TPO-Ab positive than TPO-Ab negative (237.7 vs. 12.4 IU/ml, P<0.0001) in SCH pregnant women. The mean of TPO-Ab positive was significantly more in SCH than euthyroid pregnant women (237.7 vs. 133.5 IU/ml, P= 0.0003) (Table 2, Fig 1).

Among 29 TPO-Ab positive pregnant women, the incidence of autoimmunity was significantly more in SCH than euthyroid (62.1% vs. 37.9%, p= 0.0003, RR 3.66, 95% CI 1.82 – 7.34) (Table 3, Fig 2).

The mean of thyroid hormones, cholesterol and triglycerides were compared with pregnant women with and without thyroid auto-antibodies. The mean age difference between pregnant women who were TPO-Ab positive and negative was statistically significant (23.21vs 21.94 years, P = 0.03). TSH was significantly higher in TPO-Ab positive women than TPO-Ab negative women (mean 3.15µIU/ml vs. 2.32 µIU/ml, p= 0.01). FT4 (1.15 vs. 1.18 ng/dl), Cholesterol (202 vs. 201.8 mg/dl) and triglycerides (168 vs. 161.11 mg/dl) were not influenced by antibody status with p > 0.05 (Table 4, Fig 3).

The prevalence of TPO-Ab positive was significantly more than TPO-Ab negative pregnant women with TSH 2.5 – 4.5 µIU/ml (41.4 % vs. 20.6%, P= 0.013) and with TSH >4.5 µIU/ml (20.7% vs. 5.9%, P= 0.005). The prevalence of autoimmunity was significantly more with a moderate increase in total cholesterol (89.7% vs. 72.1%, P= 0.04), although the prevalence of autoimmunity with high levels of cholesterol was more but statistically not significant (P= 0.93). The prevalence of TPO-Ab negative was significantly more with low total cholesterol levels than TPO-Ab positive pregnant women (18.1% vs. 0%, P= 0.01). There was no significant difference in prevalence of autoimmunity with triglycerides (P= 0.98) (Table 5, Fig 4).

There was a significant rise of mean values of age (23.06 vs. 21.67 years, P= 0.0009), TPO-Ab (68.73 vs. 21.28 IU/ml, P= 0.0001), and TSH (4.17 vs. 1.64 µIU/ml, P= <0.0001) in SCH than euthyroid pregnant women. There was no significant difference in mean values of FT4, cholesterol and triglycerides between SCH and euthyroid pregnant women with P >0.05 (Table 6, Fig 5). The prevalence of autoimmunity and a moderate rise of total cholesterol levels were significantly more in SCH than euthyroid pregnant women (25% vs. 6.8%, P= 0.0001 and 87.5% vs. 74.5%, P= 0.026). There was no significant difference in the prevalence of raising triglycerides between SCH and euthyroid pregnant women (41.7% vs. 42.9%, P= 0.86) (Table 7, Fig 6).

Table 1: Statistical values of thyroid and lipid parameters of study group

Statistics	Age (years)	TPO Ab (IU/ml)	TSH (µIU/ml)	FT4 (ng/dl)	Cholesterol (mg/dl)	Triglycerides (mg/dl)
Mean	22.1	35.95	2.42	1.18	202.25	161.97
SD	2.98	93.54	1.64	0.17	44.52	68.74
Lower limit	18	6	0.56	0.9	123	66
Upper limit	29	372	7.61	1.49	288	308

SD: Standard deviation; TPOAb: Thyroperoxidase antibodies; TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine

Table 2: Comparison of autoimmunity in thyroid subjects

Thyroid subjects	TPOAb positive		TPOAb negative		P value	95% CI
	N (%)	Mean± SD	N (%)	Mean± SD		
Euthyroid 161(69.1)	11 (6.8)	133.5 ± 67.63†	150 (93.2)	13.1 ± 5.2	<0.0001*	-163.1 to -77.7
SCH 72 (30.9)	18 (25)	237.7 ± 65.73†	54 (75)	12.4 ± 5	<0.0001*	-256.9 to -193.7
Total 233	29 (12.4)	198.2 ± 83.1	204 (87.6)	12.9 ± 5.2	<0.0001*	-216.3 to -154.3

SCH: Subclinical hypothyroid; SD: Standard Deviation; CI: Confidential Intervals; TPOAb: Thyroperoxidase antibodies; TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; * significance between TPOAb positive and TPOAb negative in thyroid subjects, † significance between SCH and euthyroid in TPO Ab positive pregnant women with P= 0.0003

Table 3: prevalence of TPO-Ab positive pregnant women in thyroid subjects

Total	Euthyroid N (%)	SCH N (%)	P value	Relative risk	95% CI
29	11 (37.9)	18 (62.1)	0.0003	3.66	1.82 – 7.34

SCH: Subclinical Hypothyroid; CI: confidential intervals.

Table 4: Comparison of autoimmunity with other parameters

Parameters	TPO-Ab positive Mean ± SD	TPO-Ab negative Mean ± SD	P value	95% CI
Age (Years)	23.21± 4.28	21.94 ± 2.73	0.03*	0.11 to 2.43
TSH (µIU/ml)	3.15 ± 1.88	2.32 ± 1.58	0.01*	0.2 to 1.46
FT 4 (ng/dl)	1.15 ±0.14	1.18 ± 0.17	0.37	-0.1 to 0.04
Cholesterol (mg/dl)	202 ± 38.32	201.8 ± 46.93	0.98	-17.8 to 18.2
Triglycerides (mg/dl)	168 ± 72.75	161.11 ± 68.3	0.61	-20 to 33.8

TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; TPO-Ab: Thyroperoxidase antibodies; SD: Standard deviation; CI: confidential intervals; * Significance

Table 5: Prevalence of autoimmunity with other parameters

Parameters	TPO-Ab positive	TPO-Ab negative	P value	95% CI
TSH (µIU/ml)				
2.5 – 4.5	12 (41.4)	42 (20.6)	0.013*	1.89 to 41.2
>4.5	6 (20.7)	12 (5.9)	0.005*	1.4 to 34
Cholesterol (mg/dl)				
Low (< 154)	0 (0)	37 (18.1)	0.01*	5.1 to 24
Moderate (154 – 263)	26 (89.7)	147 (72.1)	0.04*	-0.43 to 28.1
High (>263)	3 (10.3)	20 (9.8)	0.93	-9 to 17.9
Triglycerides (>160mg/dl)	12 (41.4)	84 (41.2)	0.98	-19 to 21

TPO-Ab: Thyroperoxidase antibodies; TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; SD: Standard deviation; CI: Confidential Intervals; * significant.

Table 6: Comparison of thyroid pregnant women with other parameters

Parameters	Euthyroid Mean ± SD	SCH Mean ± SD	P value	95% CI
Age (Years)	21.67 ± 2.65	23.06 ± 3.46	0.0009*	0.57 to 2.2
TPO- Ab (IU/ml)	21.28 ± 35.2	68.73 ± 103.45	<0.0001*	29.5 to 65.4
TSH (µIU/ml)	1.64 ± 0.54	4.17 ± 1.91	<0.0001*	2.2 to 2.8
FT 4 (ng/dl)	1.19 ± 0.16	1.15 ± 0.18	0.09	-0.08 to 0.006
Cholesterol (mg/dl)	201.9 ± 48.1	201.7 ± 40.7	0.98	-13 to 12.7
Triglycerides (mg/dl)	163.3 ± 71.2	159.1 ± 63.4	0.66	-23.4 to 15

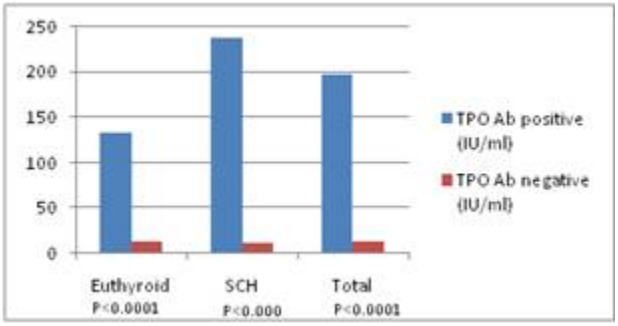
SCH: Subclinical hypothyroid; SD: Standard Deviation; CI: Confidential Intervals; TPO-Ab: Thyroperoxidase antibodies; TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; * significant.

Table 7: Prevalence of thyroid and lipid parameters between euthyroid and SCH pregnant women

Parameters	Euthyroid (161) N(%)	SCH (72) N(%)	P value	95% CI
TPO-Ab (>34 IU/ml)	11 (6.8)	18 (25)	0.0001*	7 to 29.3
Cholesterol (mg/dl)				
Low (< 154)	23 (14.3)	5 (6.9)	0.5	-7.6 to 12
Moderate (154 – 263)	120 (74.5)	63 (87.5)	0.026*	1.13 to 23
High (>263)	18 (11.2)	4 (5.5)	0.17	-3.5 to 12.8
Triglycerides (>160mg/dl)	69(42.9)	30 (41.7)	0.86	-13.3 to 15.2

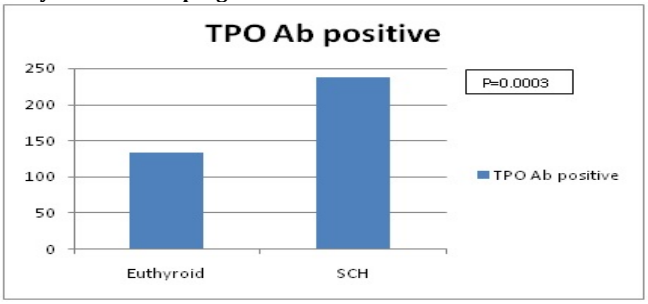
SCH: Subclinical Hypothyroid; CI: Confidential Interval.

Figure 1: Comparison of autoimmunity in thyroid subjects



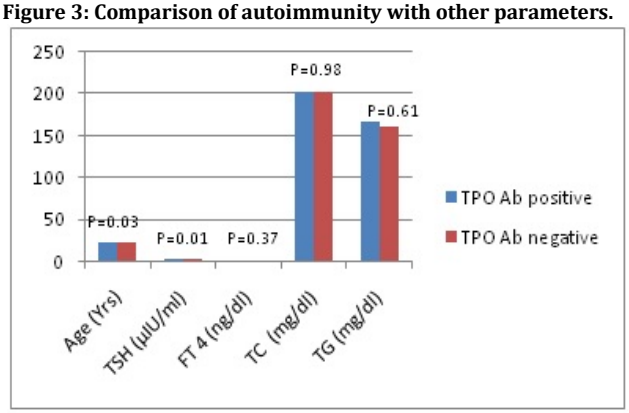
SCH: Subclinical hypothyroid; TPO-Ab: Thyroperoxidase antibodies.

Figure 2: Comparison of prevalence of TPO-Ab positive between euthyroid and SCH pregnant women



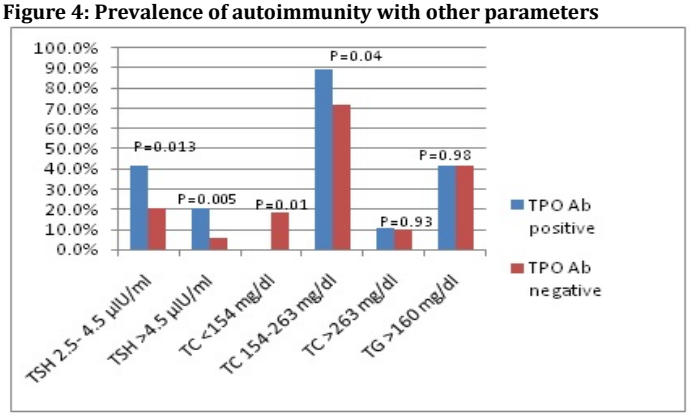
SCH: Subclinical Hypothyroid; TPO Ab: Thyroperoxidase antibodies

Figure 3: Comparison of autoimmunity with other parameters.



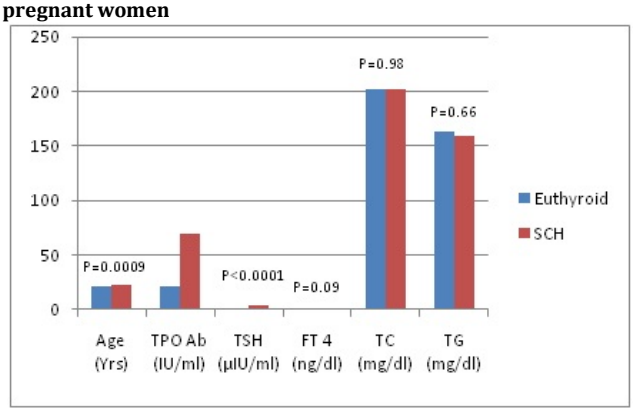
TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; TPO-Ab: Thyroperoxidase antibodies; TC: Total cholesterol; TG: triglycerides

Figure 4: Prevalence of autoimmunity with other parameters



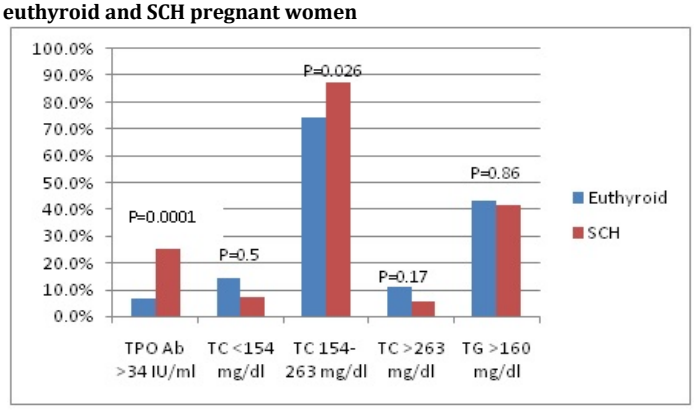
TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; TPO-Ab: Thyroperoxidase antibodies; TC: Total choleste rol; TG: triglyceride

Figure 5: Comparison of mean between euthyroid and SCH pregnant women



TSH: Thyroid Stimulating Hormone; FT 4: Free thyroxine; TPO-Ab: Thyroperoxidase antibodies; TC: Total cholesterol; TG: triglycerides.

Figure 6: Prevalence of thyroid and lipid parameters between euthyroid and SCH pregnant women



TPO-Ab: Thyroperoxidase antibodies; TC: Total cholesterol; TG: triglycerides; SCH: subclinical hypothyroid

DISCUSSION

During pregnancy, maternal thyroid hormones and cholesterol plays a vital role in the development and function of both the fetus and the placenta [8]. The lipid metabolism is more influenced by the thyroid hormone [15]. The most frequent lipid abnormality is hypercholesterolemia. Hypercholesterolemia and hypertriglyceridemia have been attributed to the hormonal effects of progesterone and estrogen. Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides [16].

Subclinical thyroid dysfunction is probably more prevalent and frequently remains undiagnosed unless specific screening programs are initiated to disclose thyroid function abnormalities in early gestation if left untreated leads to overt hypothyroidism in many cases.

As per the American Thyroid Association (ATA) guidelines for first trimester-specific reference intervals, in our study, the prevalence of euthyroid was 69.1% and among them, 6.8% were TPOAb positive with a mean value of 133.5IU/ml, higher than Ratan Chandra et al 2016 study [17] reported that 1.47% had TPO-Ab positive euthyroid women. This subgroup of the population is at increased risk of developing hypothyroidism and should be monitored every 4-6 weeks. The prevalence of SCH was 30.9% , slightly lower than the Ratan Chandra et al 2016 study [17] reported 32.9% of SCH , but much higher than other studies (3,4,18) in which the prevalence is 2.8%, 13.8%, and 10.9%, because the cutoff value of TSH>2.5 µIU/ml used to classify thyroid status. Among SCH pregnant women, 25% were TPO-Ab positive with a mean value of 237.7 IU/ml, which is much lower than the other studies with TPO-Ab prevalence of 57.1%, 57%, and 59% [3, 4, 18].

Stricker et al study [12] reported that the relative risk of thyroid autoimmunity was 4.6-fold more frequently in hypothyroid pregnant women with TSH > 3µIU/l, compared with euthyroid. In our study, the relative risk of thyroid autoimmunity was 3.66 times in SCH with TSH >2.5µIU/l than euthyroid pregnant women with p= 0.0003. According to the American Thyroid Association, 10 to 20% of all pregnant women in the first trimester of pregnancy are positive for Hashimoto's antibodies, but they are euthyroid [19]. In our study, 12.4% of pregnant women were positive for TPO-Ab, comparable with Ratan Chandra et al 2016 study [17] reported, 12.15% were TPO- Ab positive, but higher than Sieiro Netto et al study [20] reported, 5.4% were thyroid autoantibody positive.

Kontiainen et al [21] found an increase in the titer of TPOAbs with age, but this correlation was not statistically significant. In our study, there was a significant increase in TPOAbs with age. The mean serum TSH values were significantly higher in thyroid autoantibody-positive women compared to women with negative thyroid autoantibodies. This may reflect the lower thyroidal reserve during pregnancy when a greater amount of thyroid hormones is demanded. The means of FT4, cholesterol, and triglycerides were not influenced by the autoimmunity. Although the mean value of cholesterol was moderately increased, while the mean value of triglycerides was mildly increased, with reference to the normal first trimester-specific reference intervals, but statistically there

was no significant difference between TPO-Ab positive and negative pregnant women.

The prevalence of autoimmunity was significantly more with TSH >2.5 μIU/ml and with a moderate increase of cholesterol (154 -263 mg/dl). Although the prevalence of autoimmunity was more with higher cholesterol values (>263 mg/dl) but statistically not significant. There was no significant association between autoimmunity and triglycerides. The major increase in the serum cholesterol concentration is occurring in the second trimester (25 – 50%). The serum Triglyceride concentration is increasing more intensively during the third trimester (about 200 - 300%) [22].

The mean values of age, TPO-Ab, and TSH were significantly raised in SCH than euthyroid pregnant women, while no significant difference in FT4. The relationship between TSH and lipids remains controversial in SCH and euthyroid subjects. Studies reported the disturbance in the lipid metabolism in patients with SCH [23] but, the Rotterdam study reported that total cholesterol was not elevated in SCH [24]. The Colorado thyroid disease prevalence study [25] showed that TC and LDL-C in SCH were significantly higher than in euthyroidism, but TG and HDL-C were not significantly different. In euthyroid cases, Roos et al. [26] demonstrated an association between serum TSH and higher TG. A recent study shows that patients with SCH (TSH > 4,8mIU/L) have higher serum triglyceride levels and lower serum HDL-C levels than euthyroid subjects [27].

As per the American Thyroid Association (ATA) Guidelines (2011) [19] and Recent Endocrine Society guidelines [28], our study used 0.1-2.5 μIU/ml as the "reference" range for TSH values in the first trimester of pregnancy. In our study total cholesterol was moderately increased and triglyceride was mildly increased in both SCH and euthyroid pregnant women, but statistically there was no significant difference. The prevalence of autoimmunity and a moderate rise of total cholesterol levels were significantly more in SCH than euthyroid pregnant women, while there was no significant difference in the prevalence of raised triglycerides.

The American Association of Clinical Endocrinologists (AACE) recommended thyroid function screening in all women during the first trimester of pregnancy. AACE [29] and National Academy of Clinical Biochemistry (NACB) of the United States [30], recommends thyroid antibody test as the best screening test for detecting autoimmune thyroid disease, is typically the first abnormality to appear in the course of developing hypothyroidism secondary to Hashimoto's thyroiditis. The appearance of TPOAb usually precedes the development of thyroid dysfunction. Serum TSH >2.5 μIU/L in pregnant women should be used as a guide for thyroid dysfunction. To help assess the severity, it is best to also measure TT_4 or FT_4 [5]. The risk of progression to hypothyroidism could be predicted from serum TSH levels and TPO-Ab titers measured in early pregnancy. Plasma lipid profiles in the first trimester of pregnancy may predict the incidence and severity of pre-eclampsia. Hence the early recognition of moderate rise of cholesterol during early pregnancy can predict the pregnancy- related complications. This has prompted recommendations that all pregnant women should have TSH; FT4, TPOAb and lipid profile at least total cholesterol must be measured in the first trimester of their pregnancy.

This study has the limitation that only first-trimester pregnant women included; it lacks a non-pregnant control group in the same period. Further studies are recommended to second and third-trimester pregnant women to find out the progression of thyroid autoimmunity and lipid dysfunction, their effects on maternofetal outcome.

CONCLUSION

Subclinical thyroid dysfunction is probably more prevalent and frequently remains undiagnosed during early pregnancy. The relative risk of thyroid autoimmunity was increased positively with TSH >2.5 μIU/L and with moderate levels of cholesterol (154 – 263 mg/dl) in SCH than euthyroid pregnant women. Thus, all pregnant women must be screened for TPO- Ab titers, TSH, FT4 and total cholesterol during early pregnancy. These markers were useful to predict women with high-risk pregnancy during early gestation.

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