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AN OBSERVATIONAL STUDY OF PATTERN AND ASSOCIATION OF THYROID HORMONES IN VARIOUS CONDITIONS

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ABSTRACT

Background: Thyroid dysfunctions are the most common endocrine disorders seen in the population. Their signs and symptoms may be subtle, non-specific and they can be incorrectly attributed to other illnesses. This study was aimed to assess the thyroid hormones pattern in various conditions and their interrelationship. **Method:** It is a hospital based observational study conducted in 464 patients with thyroid dysfunction at an Endocrine Clinic, Hanamkonda for a period of 6 months. **Results:** Among 464 patients enrolled with thyroid dysfunction, female population were predominant (89.87%). Most prevalent thyroid disorders associated was hypothyroidism (78.01%). The mean age of the study population was 36.55 years. Of all the co morbidities associated with thyroid dysfunction, diabetes (40.51%) was found to be in higher rate. Among 180 pregnant women, hypothyroidism was the most observed thyroid dysfunction. Prevalence of both hypothyroidism (46.25%) and hyperthyroidism (56.52%) was observed predominantly in second trimester. **Conclusion:** Early diagnosis and proper management of thyroid disorders may prevent patient's risk from acquiring other co morbid conditions. Annual screening is recommended for all age groups. For pregnant women, thyroid evaluation in each trimester is beneficial.

KEYWORDS: Hypothyroidism, Diabetes, PCOS, HTN.

INTRODUCTION

Thyroid diseases are common worldwide. According to a projection from various studies on thyroid disorders, it has been estimated that about 42 million people in India suffer from

thyroid diseases. Common thyroid diseases includes hypothyroidism, hyperthyroidism, goitre and iodine deficiency disorders, hashimoto's thyroiditis and thyroid cancer.[1] Undiagnosed, improper treatment of thyroid disorders may put patients at risk for certain conditions such as diabetes, hyperlipidaemia, infertility, polycystic ovarian syndrome, hypertension, cardiovascular diseases, osteoporosis. Thyroid disorders during early pregnancy have been associated with adverse obstetric and foetal outcomes.[2]

Major disorders of the thyroid gland are hyperthyroidism and hypothyroidism, which have been reported in over 110 countries of the world with 1.6 billion people at risk and need iodine supplementation.[3] According to the American thyroid association, more than 12% of the U.S. population will develop a thyroid condition during their life time. The prevalence of hypothyroidism in India is more (11%) compared to UK (2%) and USA (4.6%).[4]

Thyroid diseases and diabetes are the two common endocriniopathies seen in the adult population. Hyperthyroidism has been associated with insulin resistance which is due to elevated glucose turnover, increased intestinal glucose absorption, elevated hepatic glucose output, and increased peripheral glucose transport accompanied by glucose utilization.[5] In hypothyroidism, the synthesis and release of insulin is decreased and the mechanisms involved are opposite to the hyperthyroidism. In overt or subclinical hypothyroidism, perputed expression of insulin mediated glucose transporter (GLUT 2) translocation may lead to insulin resistance.[5]

Rise in thyrotropin releasing hormone (TRH) in primary hypothyroidism leads to increased prolactin and thyroid stimulating hormone (TSH). Prolactin contributes toward polycystic ovarian morphology by inhibiting ovulation as a result of the change in the ratio of follicle stimulating hormone (FSH) and luteinizing hormone and increased dehydroepiandrosterone from the adrenal gland. Increased TSH levels contribute to spill over effect on FSH receptors and also collagen deposition in ovaries.[6]

Hypothyroidism is usually associated with peripheral vasodilatation and reduction of the diastolic blood pressure (BP). Fluid retention and extracellular fluid expansion in hypothyroidism might be the mechanism of hypertension (HTN).[7]

Thyroid dysfunction particularly hypothyroidism is associated with dyslipidaemia.[8] Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in LDL

because of a decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver. TG level is also increased in both overt and subclinical hypothyroidism which is attributable to the decreased activity of lipoprotein lipase that is responsible for the clearance of triglyceride rich lipoprotein. In subclinical hyperthyroidism, TC and LDL levels were slightly increased.[8]

Maternal thyroid function changes during pregnancy and inadequate adaptation to these changes results in thyroid dysfunction. These changes are a result of various factors like increase in thyroglobulin due to elevated oestrogen and human chorionic gonadotropin, increase renal losses of iodine due to increase in glomerular filtration rate, modifications in peripheral metabolism of maternal thyroid hormone and modifications in iodine transfer to placenta. The commonest cause (85 %) being Graves' hyperthyroidism, due to thyroid stimulation by thyrotropin receptor antibodies (TRabs). Deterioration in the first trimester may be due to increasing TRabs together with high levels of HCG.[9]

MATERIALS AND METHODS

Our study was conducted for a period of 6 months and the data was collected at a Endocrine Clinic, Hanamkonda regarding demographics, past medical history, laboratory parameters includes FBS, PLBS, LH, FSH, TC, TG, T3, T4, TSH and blood pressure in a specially designed data collection form.

Study criteria

Inclusion criteria

- Patients diagnosed with thyroid dysfunction along with other co morbid conditions such as diabetes (type I and type II), hypertension, Hyperlipidaemia, polycystic ovarian disease.
- Pregnant women with thyroid dysfunction.
- Patients of all age groups and both genders.

Exclusion criteria

- Patients with thyroid dysfunction without any co morbid conditions

Patients matching for study criteria were identified by regular review of patient's records during study period and documented in a predesigned data collection form. The collected data was entered into Microsoft excel database and subjected for further analysis.

Statistical analysis: Data was analysed using Pearson's correlation method in Graph pad prism software version7 to determine the correlation between thyroid hormones and other co morbid conditions where ever required.

RESULTS

A total of 464 patients were included in the study. Among them, female were 417 (89.87%), and 47 (10.12%) were male.

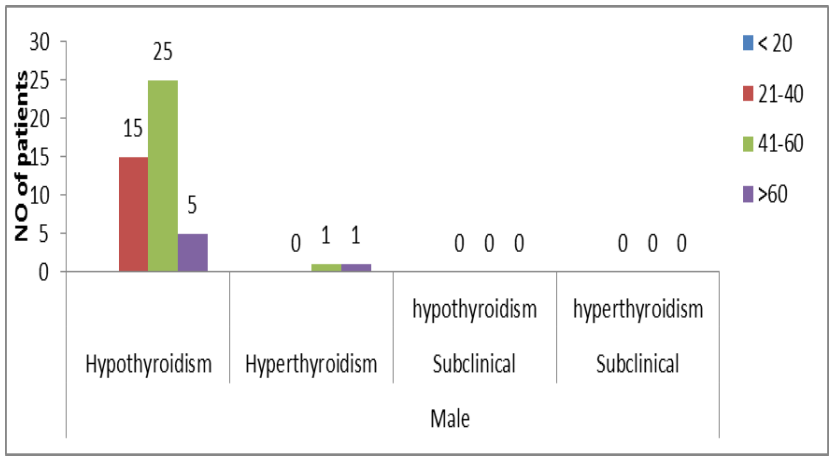

Figure 1: Distribution of data according to age groups in Male.

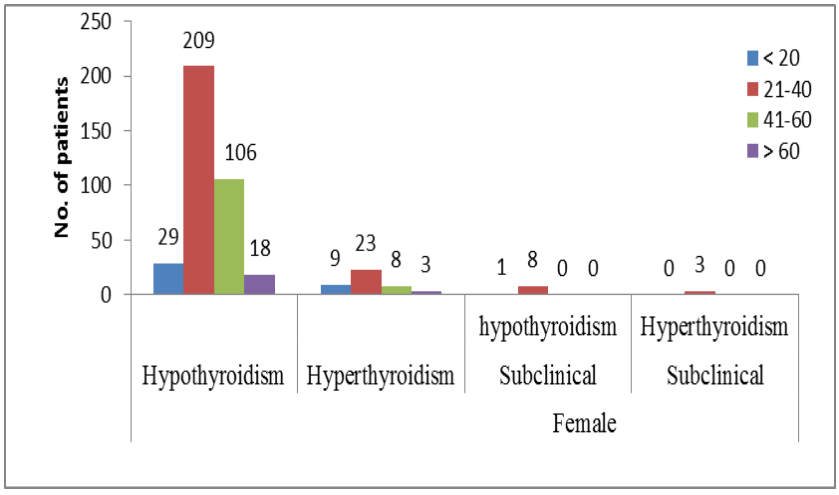

Figure 2: Distribution of data according to age groups in Female.

Of 47 male patients, hypothyroidism was found to be high between the age group of 41-60 (53.19%). Hyperthyroidism was found to be equal in the age group of 41-60 and above 60 yrs age group. In female, most of the thyroid disorders were found between age group of 21-40 years. Of these patients, 5.51% were hyperthyroid, 50.11% were hypothyroid and 1.91 subclinical hyperthyroid.

Table 1: Distribution of Data According to Various Conditions With Specific Thyroid Dysfunction.

S. No	Condition	Hypothyroidism	Hyperthyroidism	Subclinical hypothyroidism	Subclinical Hyperthyroidism
1.	DM	179	09	00	00
2.	HTN	33	13	00	00
3.	PCOS	22	00	00	01
4.	Pregnancy	146	23	09	02
5.	Hyperlipidaemia	27	00	00	00

Out of 464 patients with thyroid dysfunction, DM was found to be predominant co morbidity comprising 40.51% followed by hypertension 9.91%, Hyperlipidaemia 5.81%, PCOS 4.95%. The prevalence of thyroid dysfunction in pregnant women (38.79%) was lower than DM, but higher than remaining conditions.

Table 2: TSH Pattern Among Pregnant Women With Thyroid Dysfunction (hypothyroidism) in Each Trimester.

S. No.	Trimester	TSH (µIU/ml)			Total number of patients	%
		≤ 0.4	0.5-4.2	> 4.2		
1.	First	00	11	44	55	37.41%
2.	Second	03	22	43	68	46.25%
3.	Third	00	11	12	23	16.32%

Out of 146 pregnant women with hypothyroidism, 55 were in first trimester, 8 in second trimester and 24 were in third trimester. Among these, higher number of patients with TSH abnormality was seen in first trimester.

Table 3: T3 and T4 Pattern Among Pregnant Women With Thyroid Dysfunction (hyperthyroidism) in Each Trimester.

S. No.	Trimester	T3(ug/dl)			T4 (ng/ml)			Total number of patients	%
		≤0.7	0.8-2.5	>2.5	≤4.6	4.7-12.5	>12.5		
1.	First	00	05	00	00	02	03	05	21.73%
2.	Second	00	09	04	00	01	12	13	56.52%
3.	Third	00	05	00	00	03	02	05	21.73%

Out of 23 pregnant women with hyperthyroidism, 5 were in first trimester, 13 & 5 were in second and third trimesters respectively. Abnormal T3, T4 levels were observed mostly in second trimester.

The higher prevalence of subclinical hypothyroidism was seen in first trimester. Two pregnant women with subclinical hyperthyroidism were found to have normal T3 and T4 and low TSH.

Table 4: Thyroid hormones pattern and other parameters of investigation among diabetic patients with thyroid dysfunction. (Mean values).

S. No.	Parameters	Hypothyroid with DM-II	Hyperthyroid with DM-II	Hypothyroid with IDDM	Hyperthyroid with IDDM
1.	Age (years)	48.56	48.7	16	16.5
2.	Weight (Kgs)	68.15	55.57	40.83	37
3.	T3 (ug/ml)	O.99	2.12	0.90	0.86
4.	T4 (ng/ml)	8.54	11.71	7.9	7.65
5.	TSH (µIU/ml)	10.61	1.04	26.68	0.77
6.	FBS (mg/dl)	149.23	133.85	312.83	162
7.	PLBS (mg/dl)	216.04	223.42	368.66	198

Table 5: Thyroid hormones pattern and other parameters of investigation in Hypertensive and Hyperlipidaemia patients with thyroid dysfunction. (Mean values).

S. No.	Parameters	Hyperthyroid with HTN	Hypothyroid with HTN
1.	Age (years)	48.46	46.60
2.	Weight (Kgs)	58.46	70.06
3.	T3 (ug/ml)	3.00	0.94
4.	T4 (ng/ml)	15.38	7.64
5.	TSH (µIU/ml)	0.65	12.28
6.	SBP (mmHg)	143.38	135.12
7.	DBP (mmHg)	84.84	84.06

Table 6: Thyroid hormones pattern and other parameters of investigation in thyroid dysfunction patients with Hyperlipidaemia. (Mean values)

S. No.	Parameters	Hypothyroid with Hyperlipidaemia
1.	Age (years)	35.25
2.	Weight(Kgs)	72.14
3.	T3 (ug/ml)	1.17
4.	T4 (ng/ml)	9.12
5.	TSH (µIU/ml)	18.35
6.	TC (mg/dl)	179.5
7.	TG (mg/dl)	213

Hyperlipidaemia was observed equally in diabetic patients with hypothyroidism (27 patients), and also non diabetic hypothyroid patients (27 patients).

Table 7: Thyroid hormones pattern and other parameters of investigation in PCOS patients with thyroid dysfunction (Mean values).

S. No.	Parameters	Hypothyroid with PCOS	Hyperthyroid with PCOS
1.	Age (years)	24.59	27
2.	Weight (Kgs)	62.65	47
3.	T3 (ug/ml)	1.06	1.54
4.	T4 (ng/ml)	8.6	9.3
5.	TSH (µIU/ml)	15.4	0.01
6.	LH (IU/ml)	16.89	28
7.	FSH (IU/ml)	8.07	6.31

Table 8: Thyroid hormones pattern in pregnant women with thyroid dysfunction. (Mean values).

S. No.	Parameters	Hypothyroid with Pregnancy	Hyperthyroid with Pregnancy	Subclinical hypothyroid with Pregnancy	Subclinical hyperthyroid with Pregnancy
1.	Age (years)	24.51	24.69	23.5	22
2.	Weight (Kgs)	55.79	53.65	54.1	55
3.	T3 (ug/ml)	1.19	2.03	0.98	2.26
4.	T4 (ng/ml)	8.55	14.28	9.56	10.99
5.	TSH (µIU/ml)	15.77	0.70	8.02	0.06

Table 9: Association of TSH with different parameters of other co morbid conditions in hypothyroid patients.

S. No.	No. of patients with hypothyroidism having TSH > 4.2 µIU/ml.	Co morbidities	Association of parameters (No. of patients having > normal range)	
			Parameter 1	Parameter 2
1	95(54.91 %)	DM-II	FBS-65	PLBS-81
2	17(51.51 %)	HTN	SBP-09	DBP-03
3	18(66.66 %)	Hyperlipidaemia	TC-08	TG-15
4	18(81.81 %)	PCOS	LH-02	FSH-00

Among 95 diabetic patients with TSH >4.2µIU/ml 65 patients had abnormal FBS and 81 patients had abnormal PLBS levels.

Out of 7 hyperthyroid patients with type 2 DM, single patient was found to have increased T3 hormone with glycaemic control. In association to hyperthyroidism with HTN, among 13 patients 6 patients had abnormal T3 and 8 patients had abnormal T4 levels with half of the patients having increased systolic blood pressure.

Table 10: Correlation between thyroid hormones with FBS and PLBS.

Correlation	FBS		PLBS	
	R	P (Two tailed)	R	P(Two tailed)
T3	-0.04809	0.5298	-0.03426	0.6545
T4	-0.1796*	0.0180	-0.1423	0.0619
TSH	0.2566***	0.0007	0.2289**	0.0025

In hypothyroid with diabetes patients FBS and PLBS was showed positive correlation with TSH (r = 0.2566, p = 0.0007). Co-relation is significant at 0.05 levels (2 tailed).

We performed correlation between thyroid hormones and all included parameters but the significant correlation observed between TSH with FBS and PLBS, T4 with FBS.

Table 11: Association of duration of thyroid dysfunction with other co morbid conditions in hypothyroid patients (patients diagnosed with hypothyroidism before diagnosed with respective co morbid condition was observed).

S. No.	Duration of hypothyroidism (In years)	Total number of patients with DM	Total number of patients with HTN	Total number of patients with PCOS	Total number of patients with Hyperlipidaemia
1.	0-5	51	06	15	15
2.	6-10	24	04	00	07
3.	> 10	20	03	00	00
4.	At a time	02	09	08	05

DM was found to be the most predominant co morbid condition with hypothyroidism that was observed highly in patients having 0-5 year's duration of hypothyroidism. Between 0-5 year's duration of hyperthyroidism, three patients had DM and three patients had HTN. Among 6-10 years, two patients had DM.

DISCUSSION

Among 464 patients, female (89.87 %) were predominant over male which is similar to the study done by Deepthi govindankutty *et al.*[10] As women are more susceptible and their body is very sensitive to any hormonal changes; they react sharper than male physiological system.[11] Majority of the study population (irrelevant of the gender) were found to be hypothyroid. The most affecting age group was found to be 21-40 years in female group & 41-60 years in male. These observations were contrast to the study done by Dirty banyan *et al.*[12] Might be the reason was most of our data consistent with pregnancy condition, so higher prevalence was observed in between 21-40 years age group.

The major co morbidity associated was diabetes comprising 40.51% of the study population. Other conditions observed were pregnancy 38.79%, hypertension 9.91%, hyperlipidaemia 5.81% and PCOS 4.95%.

Among 188 diabetic patients with thyroid dysfunction 179 patients had hypothyroidism & 9 patients had hyperthyroidism. Out of 179 hypothyroid patients with DM, 173 patients were with T2DM and remaining 6 patients were with IDDM. Among 9 hyperthyroid patients with diabetes, 7 patients had T2DM & 2 had IDDM. This observation was consistent with the study conducted by Abhay Tirkey *et al.*[13] In 173 Hypothyroid patients with T2DM, 95 patients were observed with abnormal TSH and their blood glucose levels were not in control, these observations were similar to the study conducted by Yasmin *et al.*[14] The hypo and hyper-functioning of thyroid gland may influence the carbohydrate metabolism at the pancreatic islets and glucose-utilizing target tissues, where parallel autoimmune pathogenesis is very highly suspected.[15] Minor thyroid function alteration is also associates with DM.[14] On performing Pearson's correlation, significant correlation was observed between TSH with FBS and PLBS, T4 with FBS. These results were consistent with the study done by Magda Abdullah agarib.[16]

Among 46 hypertensive patients who were suffering from thyroid dysfunction, 33 were found to have hypothyroidism and 13 patients with hyperthyroidism. In 33 hypothyroid hypertensive patients, 17 patients were found to be with abnormal TSH range. Among them < 130mmHg SBP, < 90mmHg DBP was found to be in 16 (48.48%) and 25 patients (75.75%) respectively. SBP (> 130 mmHg) and DBP (> 90mmHg) was found to be in 17 (51.51%) and 08 patients (24.24%) respectively. These findings were similar to the study conducted by Gireesh AS.[17] The mechanism may be due to fluid retention and extracellular fluid volume expansion in hypothyroid patients which causes HTN,[7] and deficiency of thyroid hormones causes an acceleration of structural changes of vascular tissue increasing total peripheral resistance. Due to decreased thyroid hormone levels alteration of autonomic nervous function, leads to increase in plasma nor-epinephrine concentration (increased secretion, decreased metabolism). Increased TSH along with PRL in hypothyroid patients, suggest a reduced dopaminergic activity in central nervous system leading to high BP by increased norepinephrine levels.[18]

Of 13 hyperthyroid patients with HTN, 6 patients had abnormal T3 and 8 patients had abnormal T4 levels. Of hypertensive group, 8 patients had >130mmHg of SBP and 2 patients

had >90 mmHg of DBP respectively. Hyperthyroidism is usually associated with peripheral vasodilatation and reduction of the diastolic blood pressure, sometimes systolic also.[7]

In our study hyperlipidaemia was observed only with hypothyroidism i.e., in 27 patients. 18 patients were found to have abnormal TSH and they are mostly associated with hypertriglyceridemia and this was contrast to the study done by Cabral *et al.*,[8] Decreased thyroid secretion greatly increases the plasma concentration of triglycerides; hypertriglyceridemia in hypothyroidism is due to decreased activity of lipoprotein lipase (LPL), which results in decreased clearance of triglyceride-rich lipoproteins. In hypothyroid patients, despite the reduced activity of HMG CoA reductase, there is often an increase in the serum total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol and intermediate density lipoprotein (IDL) cholesterol. Decreased thyroid secretion greatly increases the plasma concentration of cholesterol because of decreased rate of cholesterol secretion in the bile and consequent diminished loss in the feces due to decreased number of low density lipoprotein receptors on liver cells. Decreased activity of LDL receptors resulting in decreased receptor-mediated catabolism of LDL and IDL is the main cause of the hypercholesterolemia observed in hypothyroidism.[19]

The prevalence of hypothyroidism with PCOS was found to be 22.5-27%. According to Simona gaberscek *et al.*,[20] prevalence was less compared to our study. In a total of 23 PCOS patients with thyroid dysfunction, 22 patients had hypothyroidism and single patient had subclinical hyperthyroidism. Out of 22 patients, 18 patients (81.81%) were found to have their TSH level above 4.2µIU/ml, in which 4 patients were with abnormal LH. In hypothyroidism plasma binding activity of SHBG is decreased, which results in plasma concentration of testosterone, altered metabolism of these gonadal steroids disappears when a euthyroid state is restored. The gonadotropins levels usually remain normal in hypothyroidism.[23]

Among 180 pregnant women included in the study, 146 were with hypothyroidism, 23 were hyperthyroidism, 9 were with subclinical hypothyroidism and two subjects had subclinical hyperthyroidism. This observations were similar to the study was performed by Kh paikhomba singh, *et al.*,[21] In our study a total of 146 pregnant women had hypothyroidism. Of these patients, 55 patients (37.41%) were in first trimester, 68 (46.25%) were in second trimester and 23 patients (16.32%) were in third trimester. In subclinical hypothyroidism category, of 09 pregnant women, 4 (44.44%), 3 (33.33%) and 2 (22.22%) were found to be in

first, second and third trimesters respectively. In 23 pregnant women with hyperthyroidism, 05 (21.73%), 13 (56.52%), 05 (21.73%) were found to be in first, second and third trimesters respectively. Human chorionic gonadotropin (hCG) hormone can stimulate TSH receptors, with subsequent release of T3 and T4 from follicular thyroid cells during the first trimester. Thyroid hormones have negative feedback mechanism on the pituitary gland and thus decrease TSH levels. High estrogen levels induced by hCG may markedly decrease free T3 and T4 levels by increasing their transport proteins. As a result, TSH is expected to increase, contradicting the thyrotrophic action of hCG. In some conditions TSH is expected to increase as a compensatory mechanism for decreased T3 and T4.[22]

407 hypothyroid subjects, the mean TSH (µIU/ml) in IDDM patients was found to be (26.68), as per type two diabetics patients value is 10.61, in hypertensive patients value determined as 12.28, it will be 15.4 in PCOS patients, 15.57 in pregnancy category and hyperlipidaemic patients mean value as 18.34. Thus the mean TSH was found to be high in hypothyroid IDDM patients.

T3, T4 levles were assessed in hyperthyroid patients with various conditions. The mean T3 (ug/dl) and T4 (ng/ml) levels were found to be in IDDM patients was (0.86) (7, 65), in type two diabetes patients (2.12) (11.71), in hypertensive patients (03) (15.38), in PCOS (1.54) (9.3), in Pregnancy category was (2.03) (14.28) and in hyperlipidaemic patients was found to be (18.34). Here higher mean T3, T4 levels were observed in hypothyroid hypertensive patients.

All the co morbid conditions were observed mostly in 0-5 year's duration of thyroid dysfunctions. This may be due to lack of knowledge regarding complications that occurs along with their condition, improper care of the patients on their health leading to abnormalities in thyroid hormones (in their early days of diagnosis). Other reasons which include are non-adherence to the medications, poor healthy life style including dietary habits (adding goitrogens, consuming high sugars in their diet), lack of regular exercise etc. and production of auto anti-bodies.

Role of Clinical Pharmacist

Clinical Pharmacist plays a major role in the management and prevention of thyroid dysfunction. Management of thyroid dysfunction requires careful, patient specific dosing and continuous monitoring. These services will be provided by the clinical pharmacist as per the

requirement. The risk can be decreased by giving proper counselling to the patients regarding life style modifications include avoiding intake of goitrogenic substances (cabbage, cauliflower, soybeans and high sugar diet), doing regular physical activity (minimum of 30 min walking), avoid alcohol consumption etc., disease complications and comorbid conditions. Creating awareness about medication adherence also had strong impact on Patient's health.

Acronyms

BP	Blood Pressure
DBP	Diastolic Blood Pressure
FBS	Fasting Blood Sugar
FSH	Follicle Stimulating Hormone
GLUT2	Glucose Transporter
HcG	Human Chorionic Gonadotropin
HMG	CoA 3- Hydroxy- 3- Methylglutarylcoenzyme A
HTN	Hypertension
IDDM	Insulin Dependent Diabetes Mellitus
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
LPL	Lipoprotein Lipase
PCOS	Polycystic Ovarian Syndrome
PLBS	Post Lunch Blood Sugar
PRL	Prolactin
SBP	Systolic Blood Pressure
SHBG	Sex Hormone Binding Globulin
T2DM	Type Two Diabetes
T3	Triiodothyronine
T4	Thyroxine
TC	Total Cholesterol
TG	Triglycerides
TRabs	Thyroid Auto Antibodies
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone

CONCLUSION

The pattern and relationship between thyroid hormones in various conditions was studied. Thyroid disorders were prevalent in female. Predominant thyroid dysfunction observed was hypothyroidism and the associated conditions include diabetes followed by pregnancy. The prevalence of both hypo and hyperthyroidism was seen majorly in second trimester of pregnancy. Most of the co-morbid conditions were observed within 0-5 year's duration of thyroid dysfunction.

By creating awareness among the patients who have the history of these conditions may prevent further complications associated with thyroid dysfunction. Early diagnosis and proper management of thyroid disorders may prevent patient's risk from acquiring other co morbid conditions. Pregnant women with undiagnosed or inadequately treated thyroid dysfunction have an increased risk of miscarriage, preterm deliveries, and severe developmental problems in their children. Annual screening is recommended for all age groups. For pregnant women, thyroid evaluation in each trimester is beneficial.

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