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Study of thyroid profile among the first trimester pregnant women attending tertiary care hospital in Dharwad

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Abstract
Background: The thyroid dysfunctions are quite common endocrinal disorders seen during pregnancy and the maternal thyroid dysfunctions may go unnoticed due to nonspecific symptoms. The maternal thyroid dysfunction has an adverse impact on both maternal and fetal outcome. The evaluation of thyroid functioning during first trimester avoids complications both in mother and fetus. The present study was conducted to assess the maternal thyroid functions (T3, T4, &TSH) during first trimester of pregnancy and also to determine the proportion of thyroid dysfunction in these subjects.
Method: One hundred and thirty five apparently normal first trimester pregnant women were randomly selected in the age group of 18-45 years from obstetric outpatient department of S.D M Medical College, Dharwad. The FT3, FT4 &TSH values were estimated using chemiluminescent immune assay method and TPO antibodies for abnormal thyroid functions.
Conclusion: A high proportion of hypothyroid (15.5% hypothyroid range) was observed in first trimester of pregnancy, and hence a routine antenatal screening is suggested to diagnose the thyroid dysfunction at the earliest gestation.

Keywords: First trimester pregnancy, TSH, thyroid peroxidase antibody, thyroxine, triiodothyronine

Introduction
Thyroid gland is an important endocrine gland and plays a vital role in our life. Thyroxine is needed for cellular oxidation and neurophysiologic development. It regulates our body metabolism and hormone production [1]. Pregnancy is a physiological state, associated with significant, but reversible changes in thyroid function [2]. Pregnancy increases the demand on maternal thyroid gland. When the mother fails to cope up with the increased demands, she will develop hypothyroidism. Overt hypothyroidism is known to cause infertility and amenorrhea. But women with borderline or potential hypothyroidism present with problems due to hypothyroidism during pregnancy. Thyroid dysfunction during pregnancy includes both maternal and fetal complications. Hypothyroidism is common in pregnancy. Its prevalence is estimated at about 2-3% and 0.3- 0.5% for subclinical and overt hypothyroidism respectively [3]. The presentation of hypothyroidism is not always typical. During first trimester. Thyroid gland is an important endocrine gland and plays a vital role in our life. Thyroxine is needed for cellular oxidation and neurophysiologic development. It regulates our body metabolism and hormone production [1]. Pregnancy is a physiological state, associated with significant, but reversible changes in thyroid function [2]. Pregnancy increases the demand on maternal thyroid gland. When the mother fails to cope up with the increased demands, she will develop hypothyroidism. Overt hypothyroidism is known to cause infertility and amenorrhea. But women with borderline or potential hypothyroidism present with problems due to hypothyroidism during pregnancy. Thyroid dysfunction during pregnancy includes both maternal and fetal complications. Hypothyroidism is common in pregnancy. Its prevalence is estimated at about 2-3% and 0.3-0.5% for subclinical and overt hypothyroidism respectively [3]. The presentation of hypothyroidism is not always typical. During first trimester the fetus is reliant on Trans placental passage of maternal thyroxine, as the fetal thyroid is not fully functional until 16 weeks of gestation. Neuropsychomotor development is impaired and mean IQ scores are reduced in children born to women who had thyroid deficiency during pregnancy. Pregnancy complications include spontaneous miscarriage, gestational hypertension, placental abruption and premature delivery [4].

Hyperthyroidism is known to occur in about 0.2-0.4% of all pregnancy and the commonest cause is grave's disease. But the hyperthyroidism has to be differentiated from hyper dynamic state of pregnancy, gestational transient thyrotoxicosis. Gestational transient thyrotoxicosis is self-limiting hyperthyroid state due to stimulatory effects of beta hCG [5].

Uncontrolled hyperthyroidism in pregnancy is associated with an increased risk of severe preeclampsia and four fold risk of low birth weight deliveries. Maternal hyperthyroidism may also result in fetal and neonatal hyperthyroidism [6]. Hence the present study intends to evaluate thyroid status in apparently normal first trimester of pregnant females during their first trimester to determine the abnormalities associated with thyroid functioning at the earliest and to initiate the measures that helps in preventing both maternal and fetal adverse outcomes.

Aims and Objectives

1. Estimating proportion of thyroid dysfunction in first trimester pregnant women attending S D M medical college Dharwad OPD by thyroid profile testing.
2. Estimating TPO antibodies in women with abnormalities of thyroid profile.

Methodology

A sample of 135 first trimester pregnant women attending to OBG OPD at S D M medical college Dharwad. Women with pregnancy, confirmed by UPT were selected randomly during May 2018 to May 2019 for the study. It was assessed whether they fit in to the inclusion criteria. Informed consent was then obtained for the participant in the study. A detailed history was taken regarding the symptoms, and signs of thyroid disorders. Menstrual history, obstetric history, past history, medical history, family history, personal history

1. A thorough general physical examination with reference to Pulse, blood pressure, temperature, respiratory rate wase noted followed by cardiovascular system, Central nervous system, Respiratory system, Local Thyroid examination and abdominal examination was done.
2. Women are sent for thyroid hormone profile testing FT3, FT4 & TSH by ELISA reader method.
3. The normal range of TSH in first trimester is 0.1 -2.5 µu/dl values outside this range was considered abnormal. All such women was asked to undergo Thyroid Peroxidase antibody testing.

Inclusion criteria for the study group:

1. < 14 weeks gestation
2. Singleton pregnancy
3. Age group of 18 to 45 years.

Exclusion criteria for the study group:

1. 1.Known chronic disorders diabetes mellitus and hypertension
2. Pregnant women with known thyroid abnormalities and on treatment.
3. Pregnant women not willing to give consent

Results

Study design: A hospital based case series study conducted on 135 first trimester pregnant women, to evaluate the thyroid status in them; and also to determine any thyroid abnormalities associated with it.

A 2ml of venous blood sample was collected from the antecubital vein in all the subjects and the thyroid profile (T3, T4 and TSH) was then determined by using chemiluminescence immune assay method. The data was then tabulated and statistically analysed.

Statistical tests used are

Mean: Measure of central tendency

Median: Measure of dispersion

Independent 't' test: Was used to compare quantitative variable like T3, T4, and TSH between any two groups or characteristics or variables.

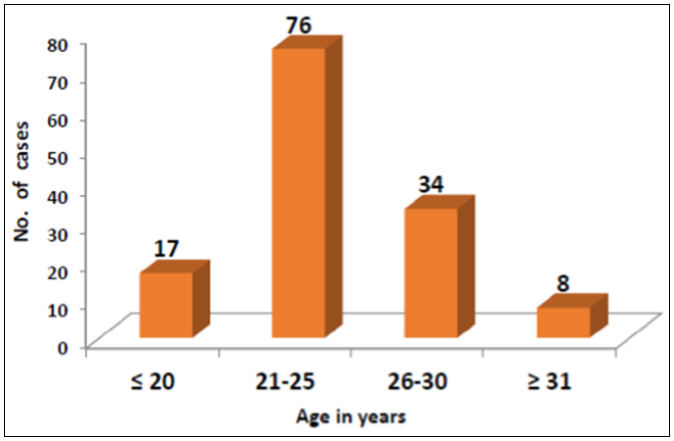
ANOVA test: Was used to compare quantitative variable like T3, T4, and TSH between any more than two groups or characteristics or variables

Table 1: Age wise distribution of cases

Age in years	No. of cases	Percentage
≤ 20	17	12.6
21-25	76	56.3
26-30	34	25.2
≥ 31	8	5.9
Total	135	100
Mean ± SD	24.5 ± 3.57	

NS = not significant, S=significant, HS = highly significant, VHS = very highly significant

Study observed that, maximum number of cases 76(56.3%) were belongs to in the age group of 21-25 years and minimum no. of cases were 8(5.9%) belong to the age group of ≥ 31. The mean and SD of age was 24.5 ± 3.57.

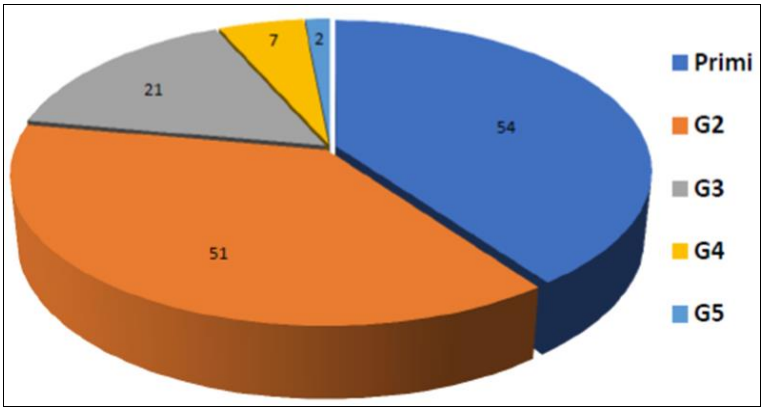


Graph 1: Simple bar diagram represents age wise distribution of cases

Table 2: Obstetrics parity wise distribution of cases

Obstetrics parity		No. of cases	Percentage
Primi		54	40.0
Multigravida	G2	51	37.8
	G3	21	15.5
	G4	7	5.2
	G5	2	1.5
Total		135	100.0

Study observed that, maximum number of cases were multigravida 81(60.0%). Out of which G2 were 51(37.8%), G3, G4 and G5 cases were 21(15.5%), 7(5.2%) and 2(1.5%) respectively. There were 54 (40.0%) of primi case.

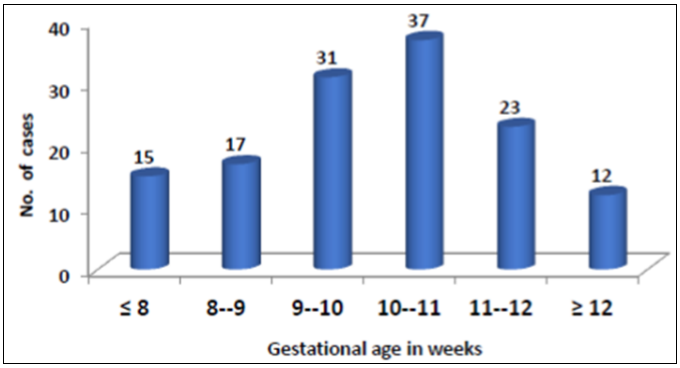


Graph 2: Pie diagram represents obstetrics parity wise distribution of cases

Table 3: Period of Gestation wise distribution of cases

POG In weeks	No. of cases	Percentage
≤ 8 weeks	15	11.1
8--9 weeks	17	12.6
9--10 weeks	31	23.0
10—11 weeks	37	27.4
11—12 weeks	23	17.0
12-14 weeks	12	8.9
Total	135	100
Mean ± SD	10.20 ± 1.43	

Study observed that, maximum number of cases 68 (50.4%) were belongs to in the gestational age group of 9--11 weeks and minimum no. of cases (8.9%) belonged to the gestational age group of ≥ 12 weeks. The mean and SD of gestational age was 10.20 ± 1.43



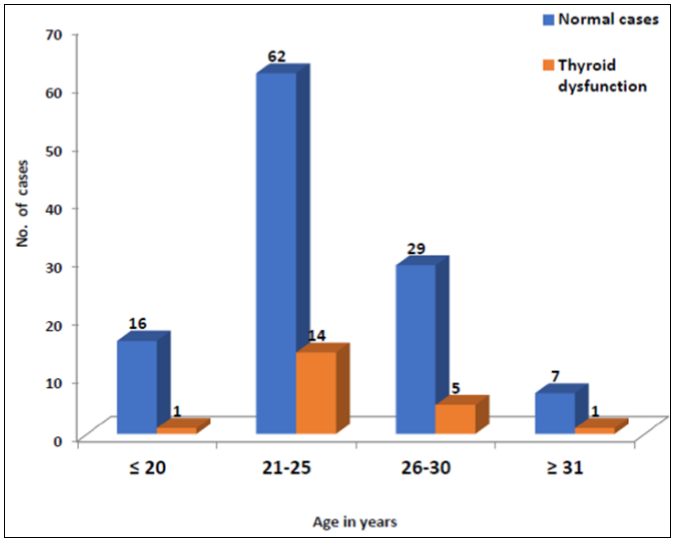
Graph 3: Simple bar diagram represents period of gestation wise distribution of cases

Table 4: Age wise comparison of normal and thyroid dysfunction cases

Age in years	Normal		Thyroid dysfunction		Total	
	No	%	No	%	No	%
<20	16	94.1	1	5.9	17	12.6
21-25	62	81.6	14	18.4	76	56.3
26-30	29	85.3	5	14.7	34	25.2
>31	7	87.5	1	12.3	8	5.9
Total	114	84.4	21	15.6	135	100
Chi-square test value P-value & Significance			X^2yates = 0.973, P>0.05, NS			

NS = not significant, S = significant, HS = highly significant, VHS = very highly significant

Study observed that, there were 21 (15.5%) of thyroid dysfunction cases in the study. The proportion of thyroid dysfunction with normal cases were 5.4:1 and the hospital incidence rate of thyroid dysfunction in first trimester pregnant women was 15.5% Study reveals that, there was no statistical significance difference of normal and thyroid dysfunction cases in relation with age (P>0.05)



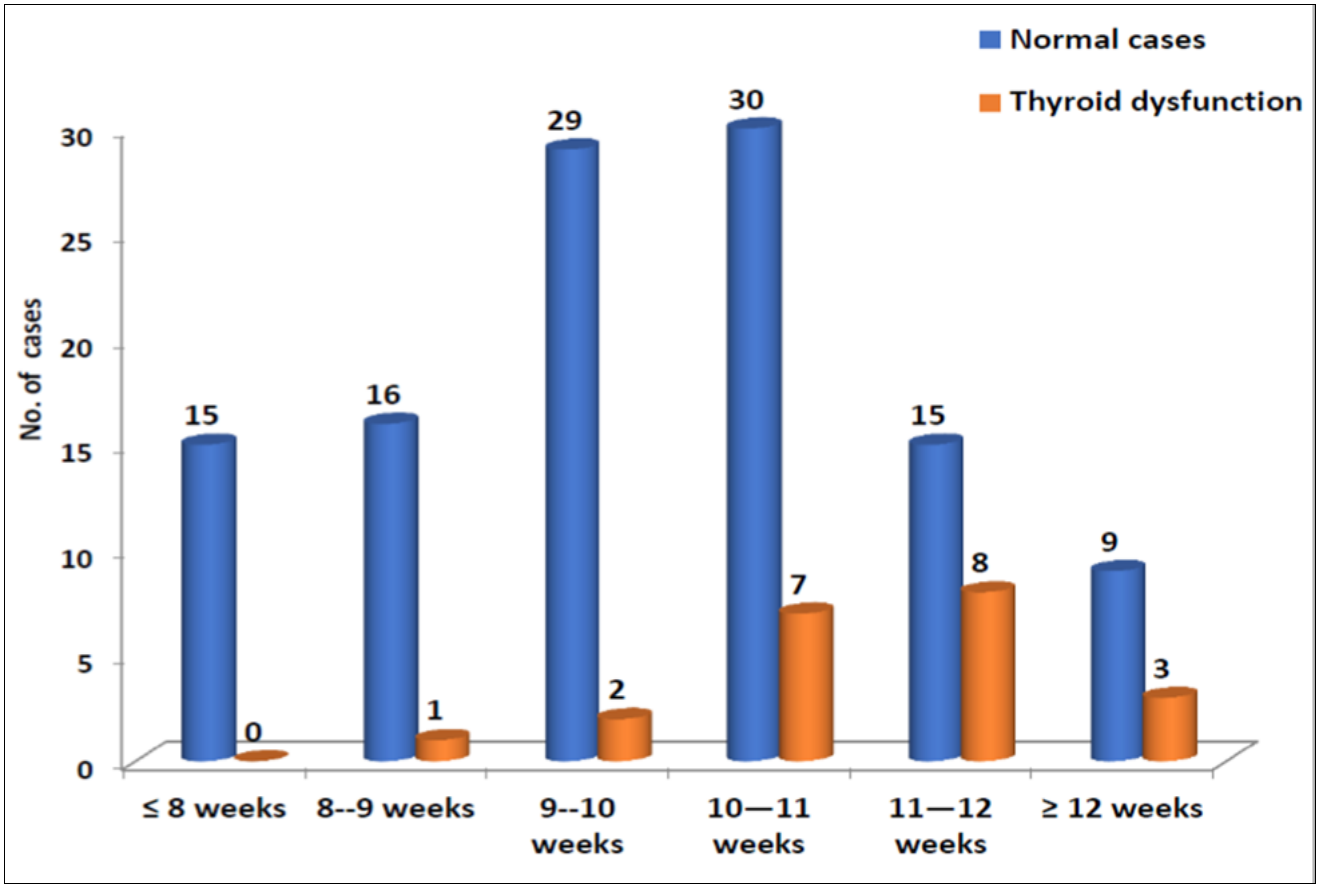
Graph 4: Multiple bar diagram represents age wise comparison of normal and thyroid dysfunction

Table 5: Comparison of Period of Gestation with normal and thyroid dysfunction

POG in weeks	Normal		Thyroid dysfunction		Total	
	No	%	No	%	No	%
≤ 8 weeks	15	100	0	0.0	15	11.1
8--9 weeks	16	94.1	1	5.9	17	12.5
9--10 weeks	29	93.5	2	6.5	31	22.9
10—11 weeks	30	81.0	7	19.0	37	27.4
11—12 weeks	15	65.2	8	34.8	23	17
≥ 12 weeks	9	75.0	3	25.0	12	8.8
TOTAL	114	84.4	21	15.6	135	100
Chi-square test value P-value & Significance			X^2 yates = 10.46, P< 0.001, VHS			

NS= not significant, S=significant, HS=highly significant, VHS=very highly significant

Study reveals that, there was statistically very highly significance association normal and thyroid dysfunction cases in relation with period of gestation (P< 0.001). Higher the period of gestation age have significantly more number of thyroid dysfunction cases as compare to lower gestation age in relation with normal cases.

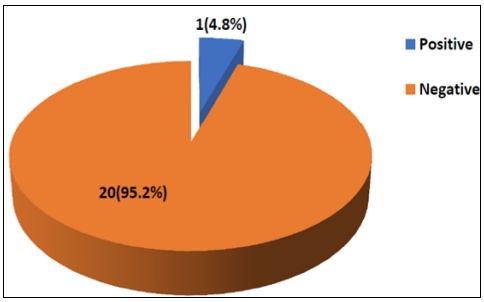


Graph 5: Multiple bar diagram represents Comparison of Period of Gestation with normal and thyroid dysfunction

Table 6: TPO wise distribution of thyroid dysfunction cases

TPO	Thyroid dysfunction	Percentage
Positive	1	4.8%
Negative	20	95.2%
Total	21	100%

Study observed that, there were 20 (95.2%) of thyroid dysfunction cases in which TPO was done and found out to be negative. Only one case 1(4.8%) had positive TPO among thyroid dysfunction in the study. In the study hospital TPO rate was 4.8%.



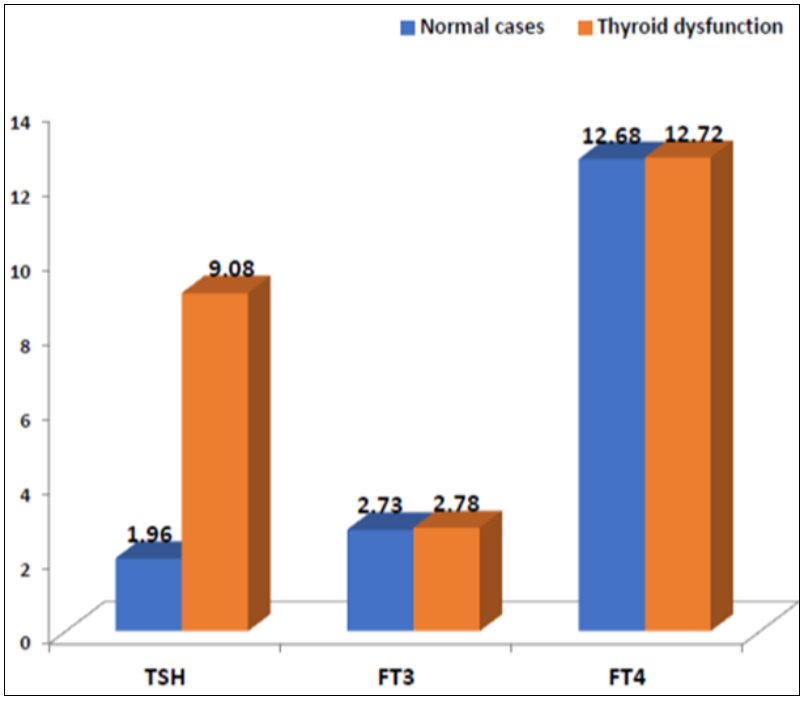
Graph 6: Pie diagram represents TPO wise distribution of thyroid dysfunction cases

Table 7: Comparison of mean TSH, FT3 and FT4 with normal and thyroid dysfunction cases

Thyroid profiles	Normal case	Thyroid dysfunction case	t- test value, P-value & Mean ± SD Mean ± SD Significance
	Mean ± SD	Mean ± SD	
TSH	1.96 ± 0.89	9.08 ± 2.31	t = 17.48 P= 0.00, VHS
FT3	2.73 ± 0.61	2.78 ± 0.73	t = 0.769 P= 0.443, NS
FT4	12.68 ± 0.90	12.72 ± 0.87	t = 0.802 P= 0.424, NS

Study reveals that, there was statistically very highly significance difference of mean TSH values among normal and thyroid dysfunction cases (P<0.001). The mean TSH values of thyroid dysfunction were significantly higher as compare with mean TSH normal values.

Study reveals that, there were no statistical significance difference of mean FT3 and FT4 values among normal and thyroid dysfunction cases (P>0.05).



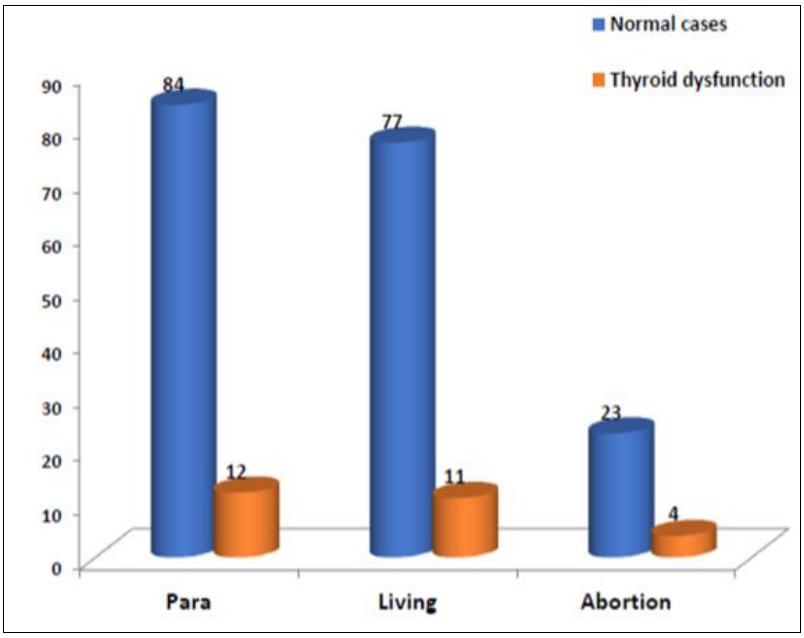
Graph 7: Multiple bar diagram represents comparison of mean TSH, FT3 and FT4 with normal and thyroid dysfunction cases

Table 8: Comparison of Para, Living and Abortion cases with normal and thyroid dysfunction cases

Variable	Normal cases (N=114)		Thyroid dysfunction Cases (N=21)		Total	Chi-square test, P-value & Significance
	No	%	No	%		
Para	84	73.7	12	57.2	96	X^2yates = 2.36, *P*>0.05, NS
Living	77	67.5	11	52.4	88	X^2yates =1.79, *P*>0.05, NS
Abortion	23	20.2	4	19.1	27	X^2yates = 0.021, *P*>0.05, NS

NS = not significant, S = significant, HS = highly significant, VHS = very highly significant

Study reveals that, there were no statistical significance difference of Para, Living and Abortions among normal and thyroid dysfunction cases (P>0.05).



Graph 8: Multiple bar diagram represents comparison of Para, Living and Abortion cases with normal and thyroid dysfunction cases

Discussion

Pregnancy can be viewed as a state, in which a combination of events occurs to modify the thyroid economy [7]. There occurs the changes in thyroid hormone levels, TSH levels and even in thyroid binding globulin levels during normal pregnancy. The thyroid dysfunction can be overlooked in pregnancy because of nonspecific symptoms and hyper metabolic state. Maternal thyroid dysfunction is associated with complications during pregnancy and can affect both the maternal and fetal outcome [8]. Therefore it is important to identify the thyroid disorders, early

in pregnancy, so that appropriate measures can be initiated.

Table 1 and graph 1 shows the age distribution of the subjects; majority of the subjects were in the age group of 21-25 years (56.3%).

Table 2 and graph 2 shows the obstetric parity wise distribution of cases. So among the study, it was observed that 54 (40%) were primigravida and 81% (60%) were multigravida. Which were divided based on number of gravidity.

Table 3 and graph 3 shows the distribution of cases based on period of gestation. From the above it was observed that 68(50.4%) were belong to in gestation age group of 9-11 weeks. This is similar to study conducted by Nambiar V [7] *et al.* which showed that mean gestational age at presentation was 10.03 ± 1.87wks.

Table 4 and graph 4 shows age wise comparision of normal and thyroid dysfunction cases, Study observed that, there were 21 (15.5%) of thyroid dysfunction cases in the study.

The proportion of thyroid dysfunction with normal cases were 5.4:1 and the hospital incidence rate of thyroid dysfunction in first trimester pregnant women was 15.5%. Study reveals that, there was no statistical significance difference of normal and thyroid dysfunction cases in relation with age (P>0.05).

Table 5 and graph 5 shows comparision of period of gestation with normal and thyroid dysfunction the Study reveals that, there was statistically very highly significance association normal and thyroid dysfunction cases in relation with period of gestation (P<0.001). Higher the period of gestation age have significantly more number of thyroid dysfunction cases as compare to lower gestation age in relation with normal cases.

Table 6 and graph 6 shows TPO wise distribution of thyroid dysfunction, Study observed that, there were 20 (95.2%) of thyroid dysfunction cases have negative TPO among thyroid dysfunction. Only one case 1(4.8%) had positive TPO among thyroid dysfunction in the study. In the study hospital TPO rate was 4.8%.

Similar study done by Dinesh K. Dhanwal, Sudha Prasad *et al.* [9], screened 1000 pregnant women in first trimester. If TSH was deranged, then free T4 and T3 and thyroid peroxidase antibody were done. Their result showed that prevalence of thyroid dysfunction was high in this study, with subclinical hypothyroidism 13.5%, overt hypothyroidism 0.7%, thyrotoxicosis 0.3% and TPO Ab was positive in 6.82% of total,18.5% of subclinical and 71% overt hypothyroid patients.

Table 7 and graph 7 shows Comparison of mean TSH, FT3 and FT4 with normal and thyroid dysfunction. Study reveals that, there was statistically very highly significance difference of mean TSH values among normal and thyroid dysfunction cases (P< 0.001). The mean TSH values of thyroid dysfunction were significantly higher as compare with mean TSH normal values. Study reveals that, there were no statistical significance difference of mean FT3 and FT4 values among normal and thyroid dysfunction cases (P value were >0.05).

Table 8 and graph 8 shows Comparison of Para, Living and Abortion cases with normal and thyroid dysfunction cases. Study reveals that, there were no statistical significance, difference of Para, Living and Abortions among normal and thyroid dysfunction cases (P>0.05).

The increase in thyroid hormone levels can be attributed to several mechanisms. During pregnancy, there is an increased concentration of estrogen which influences the increase in the synthesis of hepatic TBGs. It also prolongs the half-life of thyroid binding globulins from 15 mins to 3 days because of estrogen induced sialylation. Hence there is decreased hepatic clearance resulting in increase in total T3 and total T4 levels. During pregnancy TBG levels begin to increase after 6-8 weeks of gestation[10] and reaches a plateau around mid-gestation and remains high of about 2-3 times of preconception levels until term. Hence the levels of total T4 increase sharply between 6-12 wks of gestation, and progress more slowly thereafter and stabilize around mid-gestation. More over the changes in albumin and free fatty acid concentration which facilitates the binding of T4 and T3 to carrier proteins and lowers the concentration of free thyroid hormones levels. This leads to further stimulation of T4 and T3 synthesis [11]. The placenta secretes hCG, a glycoprotein hormone, sharing common α subunit with TSH but having unique β sub unit, which confers specificity. hCG or a molecular variant, acts as a TSH agonist, having thyrotrophic activity leads to elevated levels of thyroid hormones in first trimester which contribute to the cause of gestational transient hyperthyroxinaemia, seen in about 0.3% of pregnancies. This is commonly seen in hyperemesis gravidarum, multiple pregnancy and molar pregnancy [11]. T4 is a precursor of T3, which is major active form of thyroid hormone, T4 gets deiodinated to T3 and hence there is increased turnover of T4. This leads to relative hypothyroxemia and an increase in the production of T4 due to increased demand. About 80% of T3 produced in the body is derived extrathyroidally from T4 deiodination. T4 level is equilibrated in circulation on a manufacture and expenditure basis. Levels of thyroid hormones are determined not only by synthesis /secretion but also by their metabolism. The variations in T3 and T4 levels seems to be need based [12].

The enzyme type III deiodinase, produced by placenta, converts T4 to rT3 and T3 to diiodotyrosine and it has extremely high activity during fetal life. During fetal life as there is an increased demand for T4 and T3 hormones by the fetus, and as it mainly depends on maternal thyroid hormones in early pregnancy until 12-14weeks, it causes an increased production of these hormones which ultimately leads to an increase in circulating concentrations of the same hormone [13].

In this study out of 135 pregnant women, the 79(58.51%) subject had TSH values of <2.5μIU/ml, 34(25.18%) subjects had TSH values between 2.5-4 μIU/ml and 22(16.29%) subjects had TSH values >4 μIU/ml. This variation in TSH values can be explained by following mechanism.

Thyroid economy differs between the healthy pregnant women and healthy non pregnant women. Compared with preconceptional levels, TSH concentration is lower throughout the pregnancy. TSH is lowest in the first trimester of pregnancy [8].

The decrease in TSH level could be attributed to the thyrotrophic action of hCG, which is a thyroid regulator in normal pregnancy, because of hormone specific β subunits and extracellular receptor binding domains of hCG and TSH share multiple similarities [14].

In normal pregnancy, the placenta produces hCG in first week of conception and levels peak at week 10, before decreasing and reaching a plateau by week 20. Between 8 and 14 wks of gestation, the changes in hCG and TSH are mirror images of each other, with a significant negative correlation between the two [8]. The structural homology between hCG and TSH, where they contain a common α subunit and the hormone specific beta subunits share 85% sequence homology in first 114 amino acid and 12 cysteine residues at highly conserved position, hence their tertiary structures are very similar [15].

Therefore during first trimester of pregnancy the elevated hCG levels leads to transient increase in thyroid hormone levels and in turn causes partial suppression of TSH secretion, but not high

enough to induce overt hyperthyroidism [15]. But according to ATA guidelines, the upper limit of TSH for first trimester of pregnancy is considered as 2.5μIU/ml. Applying the same guidelines to our study population revealed the proportion of euthyroid subjects as 81.5%, 16.3% as hypothyroid (subjects had TSH values > 2.5μIU/ml), and 2.5% (subjects had TSH values < 0.04μIU/ml), as hyperthyroid. There has been a wide geographic variation in prevalence of hypothyroidism during pregnancy. It varies from 2.5% in west to 11% in India, It seems that prevalence of hypothyroidism is more in Asian countries as compared to west [16].

The present study is in agreement with the study conducted by Dinesh DK [9] *et al.*, where in the incidence of hypothyroidism was found to be 14.3% during first trimester of pregnancy. The observations of present study is similar to the study conducted by Nambier V *et al.* [7], who reported the prevalence of hypothyroidism and thyroid autoimmunity as 4.8% and 12.8% respectively.

This study is also in favour of study conducted by sahasrabuddhe A *et al.* [17] who reported the prevalence of hypothyroidism as > 10%. A study done by Mukhopadhyay A *et al.* [18] reported the incidence of hypothyroidism in pregnancy about 3.69% unlike the observations found in the present study.

A study by Goel P *et al.* [19] reported the prevalence of hypothyroidism of about 6.3% which is in favour of the findings of the present study. A study done by Shah MJ *et al.* [20] reported the prevalence of hypothyroid in 4.4% and overt hyperthyroidism in 0.6% in their study subjects which is quite less compared to the observations of the present study.

The subjects in hyperthyroid state could be due to gestational transient thyrotoxicosis (GTT) which occurs in 1-3% of pregnancies, due to elevated hCG levels or due to overt hyperthyroidism which occurs in 0.4-0.7% of pregnancies. This is in support of the fact that there is a high prevalence of gestational thyrotoxicosis in Asian women during 8-11weeks of gestation than during 12-14 weeks [21].

Conclusion

A case series study was conducted in apparently normal first trimester pregnant women to determine the thyroid status and also to assess the abnormalities associated with it.

The following conclusion can be drawn from this study.

The TSH significantly increased in the age group of 21-25 years of patient as compared to other age group considered in this study. Applying ATA guidelines for TSH values in the present study showed that 84.44% were eythyroid, 15.5% were hypothyroid among them only was TPO ab positive state.

So to conclude, the thyroid dysfunction determined based on TSH values (as per ATA guidelines) is quite high. This indicates proportion of the thyroid dysfunction present in the local population.

Further studies are required in this regard in a larger population so that gestational age specific reference intervals can also be established for local population of particular geographic area to avoid misinterpretation of thyroid function tests during first trimester of pregnancy.

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