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Thyroid Status In Different Trimesters Of Pregnant Women Attending A Tertiary Teaching Hospital In Manipur.

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Abstract: Introduction: *Maternal hypothyroidism is the most common thyroid disorder in pregnancy.Thyroid dysfunction during pregnancy has an immense impact on maternal and fetal outcome.Thyroid hormones are critical for the development of the fetal brain.Maternal hypothyroidism occurring in the first half of pregnancy might be harmful to fetal brain development.The aim of the present study was to find out the thyroid status in each trimester in normal pregnant women and to find out association of thyroid dysfunction with different trimesters.*

Material and subjects : *The cross-sectional study was undertaken in 100 pregnant women above 18 years of age irrespective of caste, creed and religion.The test was carried out in chemi - luminescence immunoassay (Diasorin LIAISON). Serum levels of TSH,T4,T3 were measured in all the study subjects.*

Results: *The mean TSH value was found to be 2.24± 2.88 mIU/mL.The mean T3 value was 1.14±0.30 /mL and that of T4 was 9.07±2.82µg/dL. Maximum number of subject with high TSH were found to be in the first trimester(14%) which falls under the category of subclinical hypothyroidism. As per American Thyroid Association 2011 guidelines,the percentage of subjects as having subclinical hypothyroidism in first,second and third trimester was 14%,2% and 2% respectively.*

Conclusion:*The maximum number of undiagnosed hypothyroidism among pregnant women was found to be in the first trimester which signifies the need for screening of thyroid function test in the first trimester for a positive fetal as well as maternal outcome.*

Keywords: *Pregnancy ,Maternal hypothyroidism, subclinical hypothyroidism*

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I. Introduction

Maternal hypothyroidism is the most common thyroid disorder in pregnancy.It has adverse effect on both mother and fetus.Maternal thyroxine is very important as the fetal thyroid gland is unable to synthesize iodothyronine until after 10weeks of gestation.From this time onwards,maternal as well as fetal thyroid hormone is critical for normal neurodevelopment.[1]Maternal and fetal thyroid insufficiency due to severe iodine deficiency causes profound neurologic impairment and mental retardation in infants.[2]Maternal hypothyroidism due to glandular failure especially inthe first trimester is associated with intellectual impairment during childhood as well as pregnancy complications like preeclampsia, placental abruption, preterm birth,low birth weight and fetal death .[3]

During pregnancy,the thyroid gland undergoes physiological changes.There is moderate enlargement of thyroid gland and increased vascularisation.Beta human chorionic gonadotropin concentration increases in the first trimester and stimulate thyroid gland due to structural similarity with TSH receptor.[4]This leads to increased free triiodothyronine (fT3) and free thyroxine (fT4),suppressing TSH secretion. Thyroid binding globulin (TBG) also increases due toestrogen stimulation. Later in second and third trimesters, the TSH subsequently normalises due to fall in beta hCG levels.Due to this physiological changes, it is important to assess the thyroid status in different trimesters of pregnant women.Also using nonpregnant reference interval in pregnancy can mislead the diagnosis and treatment of thyroid disorders during pregnancy.As discussed earlier, early maternal thyroid insufficiency, even subclinical hypothyroidism and isolated hypothyroidism have the potential to impair fetal neurodevelopment .[5] Hence, establishments of reference intervals in each trimesters of pregnancy is of utmost importance as the values will be helpful in diagnosing thyroid disorders during pregnancy.

II. Material and Methods

Study design :The study wasa cross - sectional analysis.Study location: The study was conducted at Department of Biochemistry, in the tertiary hospital , Jawaharlal Nehru Institute of Medical Sciences (JNIMS),Porompat, Manipur Study Duration: June 2017 to December 2017 Inclusion criteria: The data of 100 pregnant women above 18 years of age with singleton intrauterine gestation who gave a valid written consent who were attending the tertiary hospital for antenatal checkupwere the study group.

Exclusion criteria :

1.Pregnant women with diagnosed thyroid disorder and on thyroid medication
2.Patients with hypertension.
3.Patients with diabetes mellitus.
4.Multiple gestation .
5.History of recurrent pregnancy losses.

The study was done after getting approval from Institutional Ethics Committee. A written informed consent of the patients or their relatives was taken prior to inclusion.

Sample collection and preparation:

5ml of venous blood were collected in the plain venipuncture tube without additive or gel barrier.The blood was allowed to clot and centrifuged to separate the serum from the sample.

Assessment and analysis of thyroid profile:

Serum levels of thyroid stimulating hormone(TSH), total triiodothyronine ,TT3 and total thyroxine, TT4 of each subject was analysed. The test was carried out in chemi-luminescence immunoassay (Diasorin LIAISON) on the same day.

The method for the quantitative determination of TSH is a sandwich chemiluminescence immunoassay. Aspecific mouse monoclonal antibody is coated on the magnetic particles(solid phase); another monoclonal antibody is linked to an isoluminol derivative(isoluminol-antibody conjugate). Allassay steps and incubations are performed bytheLIAISON analyzer.

According to the 2011 guidelines of the American Thyroid Association(ATA) ,the pregnancy range of TSH are 0.1-2.5 ,0.2-3.0 and 0.3 -3.0 mIU/L in the first,second and third trimesters, respectively.[6]

Recently,the 2017 guidelines of the American Thyroid Association(ATA) recommended 4.0 mIU/L as the cut –off point for the upper limit of serum TSH in early pregnancy. [7]

Statistical analysis:

The statistical software namely SPSS 18.0, and R environment ver.3.2.2.were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs,tables etc.Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients ,

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Significant figures + Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

III. Results

Out of the total 100 pregnant women studied 34(34%) were in first trimester,36(36%) in second trimester and 30 (30%) in the third trimester respectively (Table 1). Table 3shows distribution of the subjects studied in first trimester in different ranges of thyroid function parameter.The number of pregnant women with serum TSH level >2.5 is 14(41.2%) out of the 34 pregnant women as per ATA guidelines 2011 .Also, majority of the serum level of TT3 (0.7- 1.35 ng/mL)and TT4 (5.4-11.7 ng/mL) were within normal limit. Table 4 shows distribution of subjects in second trimester in different ranges of thyroid function parameters. Only 2 (5.6% of

36) subject had high TSH level > 3mIU/L as per ATA guidelines 2011 and majority of the remaining subject in the second trimester had normal TSH level which is 34(94.4% of 36).For serum level of TT3 and TT4, majority of the subject studied were within normal range as shown in table 4.In third trimester, only 4 (13.3%) subject had high serum level of TSH while the remaining 26(86.7% of 30) were within normal range. For serum level of TT3 and TT4,most of the subject were within normal range as shown in table 5.

Thus according to ATA guideline 2011,the percentage of subclinical hypothyroidism were found to be 14% in first trimester,2% in second trimester and 4% in third trimester respectively.

Therefore, percentage of subclinical hypothyroidism were found to be maximum in first trimester which is 14% if we follow ATA 2011 guidelines for pregnancy in this study.However, if we follow the ATA guideline 2017,then percentage of subclinical hypothyroidism in first, second and third trimester is 13%,2% and 0% respectively.

So it is evident as shown in figure 1 that the ATA guideline 2011 overestimates the diagnosis of subclinical hypothyroidism in pregnancy.

Again, when we look into the levels of TT3 , it was found that 27%, 26% and 23% of the cases were having normal values in first, second and third trimester respectively as shown in figure 2.Likewise, for TT4 levels it was found that 24%,28% and 23% of the cases were having normal values in first, second and third trimester respectively as shown in figure 3.Lastly, we have table 6 in which the mean TSH level in first, second and third trimester are 3.74±4.11, 1.29±1.73, 1.69±1.17 respectively with total mean value 2.24±2.88.The differences between the four groups were statistically significant (p =0.001**). Also figure 4 shows the trimester wise distribution of Mean thyroid functions and figure 5 shows the mean thyroid functions of the total study subjects.

Table 1: Trimesterwise distribution of subjects studied

Trimester	**No. of patients**	**%**
1st	34	34.0
2nd	36	36.0
3rd	30	30.0
Total	100	100.0

Table 2: Distribution of subjects in different trimesters according to age.

Age in years	**Trimester**			**Total**
	1st	**2nd**	**3rd**	
<20	2(5.9%)	4(11.1%)	4(13.3%)	10(10%)
20-30	25(73.5%)	24(66.7%)	26(86.7%)	75(75%)
31-40	7(20.6%)	8(22.2%)	0(0%)	15(15%)
Total	34(100%)	36(100%)	30(100%)	100(100%)
Mean ± SD	26.47±4.43	26.61±4.51	25.33±3.76	26.18±4.27

Following tables and figures represent the distribution of Thyroid function parameter (TSH, TT3, TT4) of the subjects studied in 1st, 2nd and 3rdTrimesters respectively.

Table 3: Distribution of subjects in first trimester in different ranges of thyroid function parameters

VARIABLES		NUMBER OF SUBJECTS IN FIRST TRIMESTER (%) n=34
TSH mIU/L	0.1-2.5	20(58.8%)
	> 2.5	14(41.2%)
T T3 ng/mL	<0.7	1(3.0%)
	0.7 - 1.35	27(79.4%)
	>1.35	6(17.6%)
T T4 mcg/dL	<5.4	2(5.9%)
	5.4 - 11.7	24(70.6%)
	>11.7	8(23.5%)

Table 4: Distribution of the subjects in second trimester in different ranges of thyroid function parameter.

VARIABLES		NUMBER OF SUBJECTS IN SECOND TRIMESTER (%) n=36
TSH mIU/L	0.2-3.0	34(94.4%)
	> 3.0	2(5.6%)
T T3 ng/mL	<0.7	1(2.8%)
	0.7 - 1.35	26(72.2%)
	>1.35	9(25.0%)
T T4	<5.4	4(11.1%)

mcg/dL	5.4 - 11.7	28(77.8%)
	>11.7	4(11.1%)

Table 5: Distribution of the subjects in third trimester in different ranges of thyroid function parameter.

VARIABLE		NUMBER OF SUBJECTS IN THIRD TRIMESTER (%) n=30
TSH mIU/L	0.2-3.0	26(86.7%)
	> 3.0	4(13.3%)
T T3 ng/mL	<0.7	1(3.3%)
	0.7 - 1.35	23(76.7%)
	>1.35	6(20.0%)
T T4 mcg/dL	<5.4	5(16.7%)
	5.4 - 11.7	23(76.7%)
	>11.7	2(6.6%)

Figure 1compares the percentage of subjects diagnosed as having subclinical hypothyroidism as per ATA 2011 and ATA 2017 guidelines. It is evident here that the ATA 2011 guidelines over estimates the diagnosis of Subclinical hypothyroidism in pregnancy.

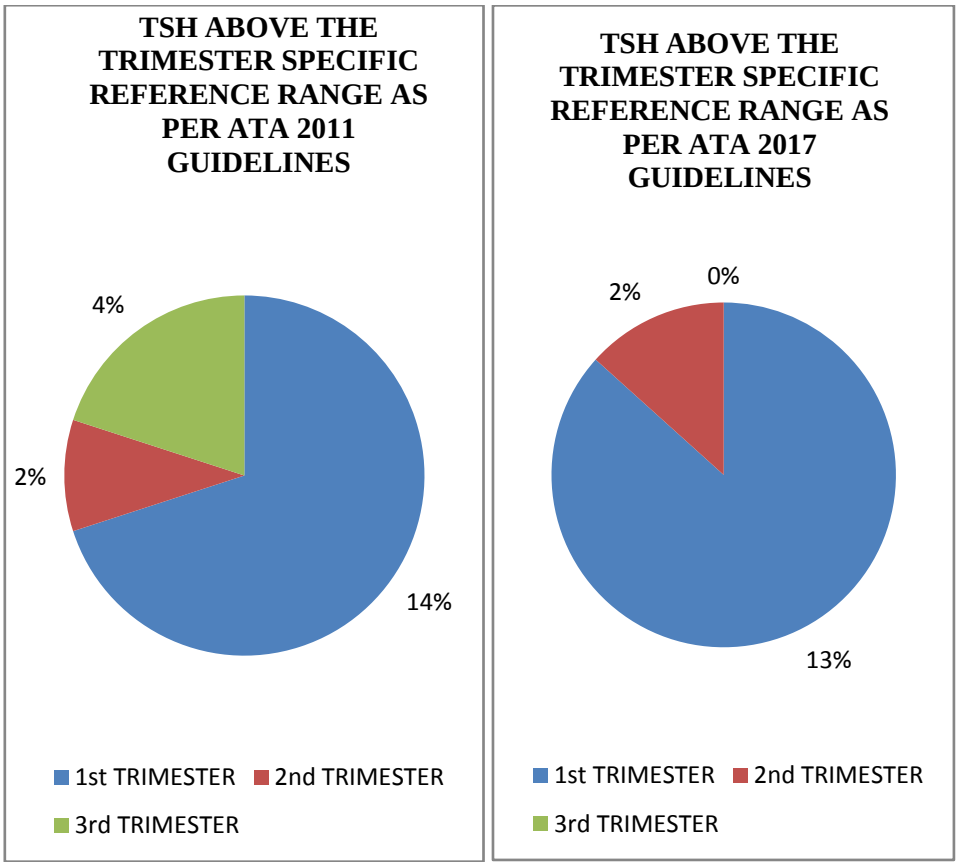

Figure1: Comparison of ATA 2011 and ATA 2017 guidelines cut-off of upper limits for Subclinical hypothyroidism in pregnancy

Figures 2 and 3 depicts the trimester-wise distribution of serum total T3 and total T4 leves respectively

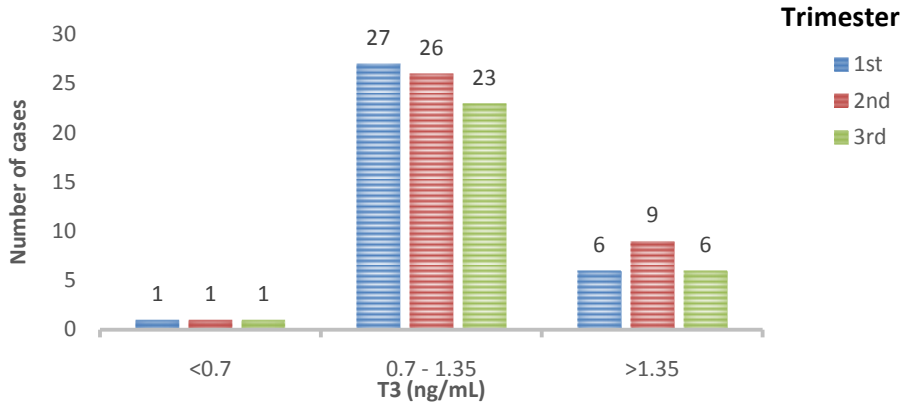

Figure2: Trimester-wise distribution of TT3 levels

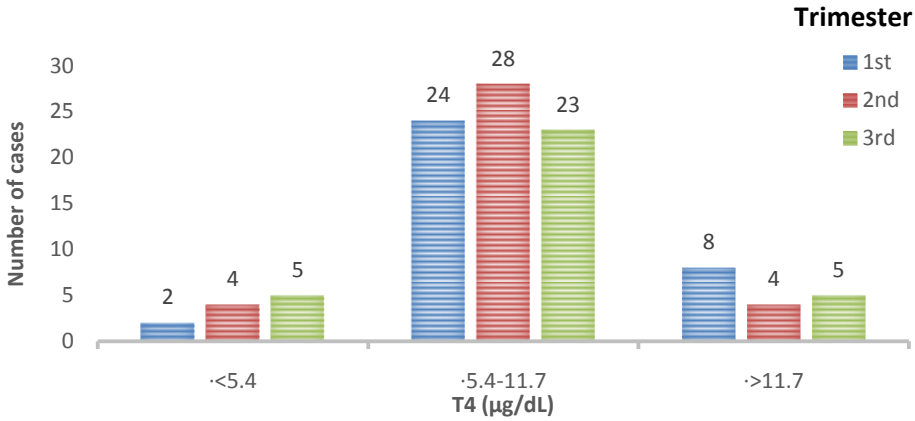

Figure3: Trimester-wise distribution of TT4 levels

Table 6, Figure 8 and 9 represents the mean thyroid functions of the subjects trimester-wise and of the total study population

Table 6: Comparison of thyroid functionparameters in relation to trimester of pregnancy as Mean±SD

variables	Trimester			Total	P value
	1st	2nd	3rd		
TSH (mIU/mL)	3.74±4.11	1.29±1.73	1.69±1.17	2.24±2.88	0.001**
T3 (ng/mL)	1.09±0.26	1.19±0.29	1.17±0.35	1.14±0.30	-
T4 (µg/dL)	9.98±2.66	9.22±2.18	7.87±3.30	9.07±2.82	-

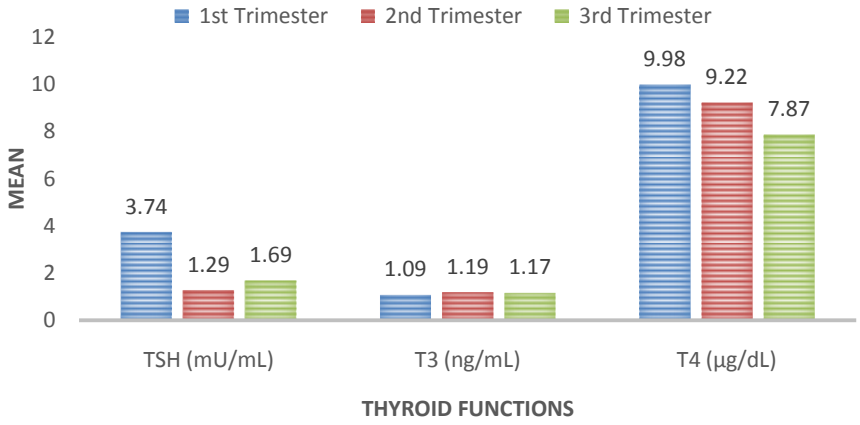

Figure4: Trimester-wise distribution of Mean thyroid functions

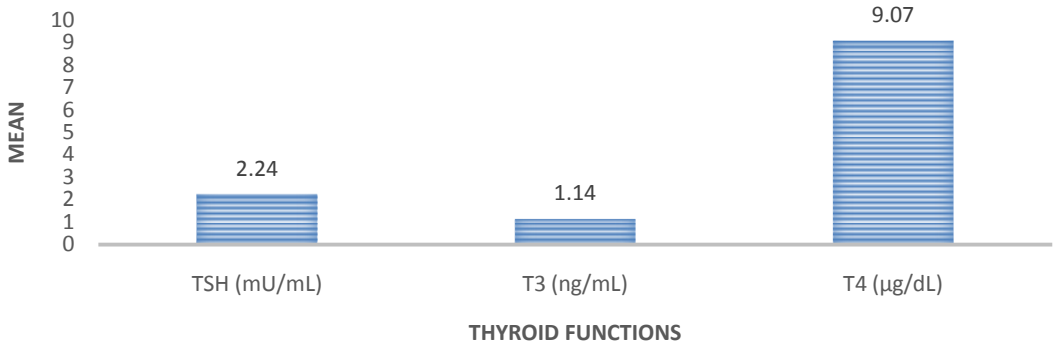

Figure5: Mean thyroid functions of total study subjects

IV. Discussion

Thyroid dysfunction found in this study fall under subclinical hypothyroidism with maximum number in the first trimester which was found to be 14%.By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficinency in patients who have few or no apparent clinical features of hypothyroidism. Biochemically, subclinical hypothyroidism has high TSH level with normal T3 and T4 level . It is the most frequent thyroid disease occurring in pregnancy. [8] The prevalence of SH varies between 1.5 and 45% from one study to another,depending on the definition of SH, ethnicity, iodine intake and study design.[9]This is in contrast with the prevalence of SH found in our study.Various reasons have been proposed for increased prevalence of hypothyroidism in pregnant women especially in sub mountain areas (Kashmir to North East India). Geo-chemical nature in deficiency of iodine and micronutrients, due to glaciations,high rain falls,floods leading to decreased iodine content in soil and water is considered to be the cause of increased prevalence of hypothyroidism in this region.[10]

During pregnancy,thyroid dysfunction has an immense impact on both maternal and fetal outcomes.[11] It is very important to note that children born to hypothyroid mothers have poor intellectual function in their later part of life.[6] Even pregnant women with very mild hypothyroidism had low IQS infants. [12]Thus ,majority of the developed countries have national neonatal screening program.[13] Also the prevalence of hypothyroidism is more in Asian countries when compared with the West, it has a variation of 2.5% in the West to 11% in India. [14]

In a study done by Sahay RK , the prevalence of subclinical hypothyroidism was found to be 2-3%.[15]Sahu MT *et al*, in their study found prevalence of subclinical hypothyroidism to be 6.47%. [16] Brian MC et al. in their study , found 2.3% as prevalence of subclinical hypothyroidism and this corresponds with virtuallyall previous reports.[17,18,19] In contrast , Rajesh Rajput, in his study found high prevalence of subclinical hypothyroidism with 21.5% in the first trimester. [20]Similar high prevalence of subclinical hypothyroidism is seen in our study too. Thus,we see variations in different studies and the possible causes already discussed above.

V. Conclusion

Subclinical hypothyroidism are very common among pregnant women in this endemic goitre region of India. There were no overt hypothyroidism probably due to small size of study population in our study. Our study had some limitations as the study subject included were only pregnant women residing in Manipur attending a tertiary hospital without considering other countries or ethnic groups and those not coming for antenatal check up. Maximum number of undiagnosed hypothyroidism among pregnant women were found to be in the first trimester. In view of the deleterious effects of hypothyroidism in pregnancy and fetus, it is of utmost importance to make universal screening of thyroid function test in first trimester mandatory.

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