ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 08 | August - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ESTABLISHMENT OF TRIMESTER SPECIFIC REFERENCE RANGES FOR THYROID FUNCTION TESTS IN SOUTH INDIAN WOMEN

Obstetrics & Gynaecology

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ABSTRACT

Introduction : To establish trimester specific thyroid profile ranges in south Indian women. **Materials And Methods:** This is a cross sectional study conducted in between 2019 and 2021. A total of 1000 pregnant women with uncomplicated singleton, intrauterine pregnancy who were consuming iodized salt were recruited for the study. A total of 274 participants with any of the predesigned exclusion criteria like family history of thyroid(161), history of abortions(74), goitre (60), anti TPO antibody(12), overt hypothyroidism (29) were excluded from the study. A total of 726 participants who met the inclusion criteria were taken for analysis including 308 (42.4%) in first trimester, 174 (24%) in second trimester and 244 (33.6%) in third trimester to derive trimester specific reference ranges of thyroid function tests by using chemiluminescence immunoassay.

Results:

The reference ranges obtained for the first, second and third trimester were

	TSH (mIU/L)	FT3 (pmol/L)	FT4(pmol/L)
I.	0.7-2.4	2-3	0.59-0.99
II.	1.2-2.8	2-3	0.48-0.95
II	1.7-3.34	2-3	0.42-0.9

Conclusion:

This study ways for the trimester specific reference intervals for thyroid function tests in regional population, thus helping in early identification of thyroid disorders in pregnant women and prevention of adverse outcomes.

KEYWORDS

Pregnancy,Trimester,Thyroid function test,Hypothyroid,Anti Thyroid peroxidase antibodies.

INTRODUCTION

Thyroid hormones are required for foetal growth and prenatal and neonatal brain development. Thyroid issues are common in pregnant women and have been linked to both maternal and foetal complications. As there are no proper trimester specific reference ranges established based on population groups, ethnicity, region, this study ways to provide trimester specific reference intervals for thyroid function tests in south Indian women.

Hyperthyroidism arises in 0.1–0.4% of pregnant women. While approximately 11% of pregnant women are hypothyroid, with 2-3% having overt hypothyroidism and 9.5% having subclinical hypothyroidism. Thyroid antibodies are found in 5–10% of pregnant women, implying that they are at an increased risk of thyroid insufficiency.

Furthermore, there is no definitive evidence that subclinical hypothyroidism has a role in the development of foetal and maternal problems. Subclinical hyperthyroidism is not linked to negative consequences. Thyroid autoimmunity appears to be linked to increased incidence of miscarriage and preterm delivery in pregnant women.

TPO antibodies are found in roughly 10% of pregnant women during the first trimester and are linked to an raised incidence of subclinical hypothyroidism in pregnancy as well as postpartum thyroid dysfunction. The latter issue affects 5-9 percent of women, with 25-30% of them developing persistent hypothyroidism. So, while screening for thyroid dysfunction and thyroid antibodies is ideal in a preconception clinic, it is certainly suggested in the early stages of pregnancy.

Aims And Objectives

The goal of this study was to find trimester-specific reference ranges for free triiodothyronine (FT(3)), free thyroxine (FT(4)), and thyroid stimulating hormone(TSH) in healthy pregnant Indian women.

METHODOLOGY

This is a cross sectional study conducted in between 2019 and 2021. A total of 1000 pregnant women with uncomplicated singleton, intrauterine pregnancy who were consuming iodized salt were recruited for the study.A total of 726 participants who met the inclusion criteria were taken for analysis including 308 (42.4%) in first trimester, 174 (24%) in second trimester and 244 (33.6%) in third trimester to derive trimester specific reference ranges of thyroid function tests by using electrochemiluminescence immunoassay.

Place of study: Government general hospital, Guntur

Sample size: 1000

Period of study: DECEMBER 2019- JUNE 2021.

Questionnaire:

A questionnaire will be drafted to investigate the general information of the participants. The details of demographic, clinical, and family history of participants were recorded, especially personal and family history of thyroid diseases, or positive thyroid autoimmune antibodies, visible or palpable goiter, abnormal function of liver, kidney or heart, and personal history of medication use.

Sample Collection:

3ml of blood samples will be obtained from each participant on the morning after overnight fast, and the isolated serum samples will be stored at 4°C. Thyroid function tests; free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb)] will be measured within 24 hours by electro chemiluminiscent assay.

Inclusion Criteria:

- Age ≥18 but ≤40 years
- No personal history of thyroid diseases
- No visible or palpable goitre
- No liver/kidney/heart dysfunction
- No family history of thyroid diseases
- No medication history of estrogen or antithyroid drugs
- Optimal iodine nutrition.

Exclusion Criteria:

- Thyroid function test, questionnaire was incomplete.
- Family h/o thyroid illness
- H/O abortion
- Goitre
- Anti thyroid peroxidase antibody
- Overt hypothyroidism
- Overt hyperthyroidism

RESULTS:

Table 1: Age

Age	frequency	Mean TSH	Mean T3	Mean T4
< 25 years	630	2.13 ±0.94	3.30 ±0.29	13.6 ± 2.12
≥25 years	370	2.74±0.70	2.85 ±0.29	10.12± 2.7
P value	-	0.001*	0.33	0.001*

The mean age observed in the present study was 23.55 ± 2.29 years. 63% of the participants were aged < 25 years and 37% were aged ≥25 years. There was a statistically significant difference in the mean values of thyroid parameters with age. TSH values were significantly higher and T4 values were lower as the age advanced.

Table 2 : Trimester wise mean, median values for each thyroid function test (total population)

TSH	Trimester	Mean ± SD	P value
	1st	2.08 ± 0.99	
	2nd	2.16 ±0.66	
	3rd	2.78± 0.78	
FT3(pmol/L)	1st	3.34± 0.30	>0.05
	2nd	3.23± 0.29	
	3rd	2.85 ±0.29	
FT4(pmol/L)	1st	13.8 ± 2.1	0.001
	2nd	13.22 ± 2.05	
	3rd	10.13 ± 2.14	

In the present study it was observed that there was a significant difference between the mean TSH, FT4 values across various trimesters of pregnancy. TSH was higher as the pregnancy progressed where the FT4 was lowered as the pregnancy advanced. Whereas it was observed that the variations in the FT3 values was not statistically significant.

Table 3 : Anti TPO positive : total 35 tested

	Frequency	TSH (mIU/L)	FT3(pmol/L)	FT4(pmol/L)
Yes	12	5.71± 1.71	2.72± 0.30	8.85± 0.12
No	23	4.4 ± 0.76	2.53 ± 0.29	8.8± 0.13
p value	-	0.001	0.83	0.85

35 subjects were tested for anti TPO antibodies and 12 were positive (titres> 34IU/L considered positive) . There was a significant association between anti TPO antibodies and TSH, T4 levels. Anti TPO antibody testing was done in very few cases with suspected thyroid dysfunction. TSH levels were significantly higher in cases with anti TPO positivity where T4 levels were low in both cases without much significance.

Table 4:Abortions

	Frequency	TSH (mIU/L)	FT3(pmol/L)	FT4(pmol/L)
Yes	12	3.64 ±1.08	2.85 ±0.30	11.16 ±2.11
No	23	2.25 ±0.87	3.16 ±0.29	12.43 ±1.13
p value	-	0.001	0.77	0.001

In the present study 7.4% of the cases had history of abortions. In the present study, there was a significant association between the thyroid profile and history of abortions. Mean TSH value was significantly higher and T4 value is decreased in cases with history of abortion when compared to those who did not had.

DISCUSSION

Thyroid dysfunction is usually seen in pregnancy and puerperium, can affect both mother & fetus(1,2). In pregnancy Hypothyroidism is more common than hyperthyroidism (prevalence 11.07% versus 2%) . Early diagnosis & necessary interventions improve maternal and fetal prognosis.

Hence using reliable trimester specific reference ranges specific for the region, for evaluation of thyroid dysfunction in pregnant women will be necessary(3).

There was a statistically significant difference in the mean values of thyroid parameters with age. TSH values were significantly higher and T4 values were lower as the age advanced There was an increase in the levels of TSH and decrease in T4 levels in women with anti TPO antibody, but its significance could not be determined from our study as TPO antibody testing was done in very few women due to cost effectiveness.

The prevalence of thyroid autoantibodies increases with age. According to NHANES III (1988-1994), the prevalence of thyroid peroxidase antibody (TPOAb) increases to 11.3% in patients' 20s, 14.2% in their 30s, and 18.0% in their 40s, and the prevalence of antithyroglobulin antibody (TgAb) increases to 9.2% in their 20s, 14.5% in their 30s, and 16.4% in their 40s.(9)The thyroid autoantibody titre decreases as gestation progresses.(10)Therefore, TPOAb measurements should be performed as early as possible during pregnancy. It is important to make sure the anti-thyroid antibody (TPOAb and/or anti-Tg) is done in cases with borderline raised TSH values. More outcome-based studies are required to know the normative data on antibody positive and antibody negative patients.

Medici et al(4) reported that serum TSH level was significantly higher and free T4 level was significantly lower in TPOAb-positive pregnant women than in TPOAb-negative pregnant women. They also reported significantly higher prevalences of subclinical and overt hypothyroidism in TPOAb-positive pregnant women than in TPOAb-negativepregnant women (subclinical hypothyroidism 20.1% vs. 2.4%, overt hypothyroidism 3.3% vs. 0.1%). Therefore, TPOAb positivity was associated with higher maternal TSH level, lower free T4 level, and 8- and 26-fold higher risks of subclinical and overt hypothyroidism, respectively. Therefore, euthyroid pregnant women who are positive for TPOAb or TgAb should have serum TSH concentration measured at pregnancy confirmation and every 4 weeks through mid-pregnancy.

In the present study it was observed that there was a significant difference between the mean TSH, FT4 values across various trimesters of pregnancy. TSH was higher as the pregnancy progressed where the FT4 was lowered as the pregnancy advanced. Whereas it was observed that the variations in the FT3 values was not statistically significant.

These findings were similar to other Indian studies. Deshwal et.al established reference gestation specific reference ranges for pregnant women in Dehradun, FT3, FT4 and TSH in the first trimester of pregnant showed 07.40±1.26 pmol/L, 14.20±1.75 pmol/L and 01.41±0.93 mIU/L respectively. Second trimester of pregnant FT3, FT4 and TSH was 04.05±1.13 pmol/L, 12.02±2.01 pmol/L and 01.56±0.86 mIU/L and third trimester of pregnant FT3, FT4 and TSH was 02.92±0.93 pmol/L, 07.96±1.78 pmol/L and 02.73±0.63 mIU/L respectively. The study suggests that FT3 and FT4 gradually reduced from first trimester to third which showed that fetus and mother required more thyroid hormones(5) The reference values in our study are similar to a study by Rajput et.al done in Haryana showed 2.5th–97.5th percentiles for FT3, FT4, and TSH obtained as 2.53–4.54 pmol/L, 16.6±2.9 pmol/L and 0.37–3.69 mIU/L in the first trimester, 2.0–4.73 pmol/L, 15.57± 33 and 0.54–4.47 mIU/L in the second trimester, 2.01–4.01 pmol/L, 15.57±1.41 pmol/L and 0.70–4.64 mIU/L in the third trimester of pregnancy.

Mean TSH increased and mean FT3 decreased significantly with the progression of gestational period. FT4decreased from trimester 1st to 3rd, but the decrease was non-significant from 2nd to 3rd trimester(6) In 2011, the ATA suggested reference ranges for serum TSH of 0.1-2.5 mU/L in the 1st trimester, 0.2-3.0 mU/L in the 2nd trimester, and 0.3-3.0 mU/L in the 3rd trimester. An upward shift in the reference upper limit of TSH was also supported by studies in other countries.(11,12) In addition, the analysis of serum TSH and free T4 “set-point” in pregnant women showed that reductions in free T4 were observed only when serum TSH was greater than 4.8 mU/L. Therefore, in 2017, the ATA revised the TSH reference range to 0.5-4.0 mU/L in pregnant women if there is no country-specific range.(8)According to this, thyroid hormone (L-T4) therapy is recommended for TPOAb-positive women with serum TSH >4.0 mU/L and TPOAb- negative women with serum TSH >10.0 mU/L. It may be considered for TPOAb-positive women with serum TSH >2.5 mU/L and TPOAb-negative women with serum TSH >4.0 mU/L. However, considering the frequency of miscarriage increased in TPOAb-positive women with

serum TSH >2.5 mU/L and it is worth considering that L- T4 therapy starts at a serum TSH of 2.5 mU/L or higher(7)

CONCLUSION

Before the introduction of screening for thyroid dysfunction in pregnancy, it is definitely necessary to establish the trimester specific reference levels of thyroid hormones based on ethnic background, regional factors like iodine status, calculation methods. This study ways for the trimester specific reference intervals for thyroid function tests in regional population, thus helping in early identification of thyroid disorders in pregnant women and prevention of adverse outcomes.

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