

Original Research Article

Thyroid hormones reference ranges during each trimester of normal pregnancy subjects in Andhra Pradesh, South India

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ABSTRACT

Background: The Thyroid hormones normal levels are very much essential for fetal neural development and good pregnancy outcome. Thyroid insufficiency during pregnancy may be associated with adverse obstetric outcome and fetal neurodevelopmental deficits. The main objective of the study is to estimate and establish the reference ranges of thyroid hormones as it varies from place to place and inter dependent on the iodine levels as the American Thyroid Association strongly recommends to refer to population defined trimester-specific reference ranges.

Methods: A longitudinal study was conducted at obstetric clinic, Kakinada city, Andhra Pradesh over a period of 18 months. The total number of normal pregnancy subjects included in this study was 126. Thyroid hormones estimation was done by Competitive electrochemiluminescence (T3 and T4) and Sandwich electrochemiluminescence (TSH) at Thyrocare Laboratory. Only 47 subjects were having all three trimester thyroid hormone levels estimated during each trimester and were followed up to full term. The 2.5th and 97.5th percentiles were calculated as the reference intervals for thyroid hormone levels during each trimester.

Results: The thyroid hormone levels during first, second and third trimesters median with reference intervals - Total Triiodothyronine (T3) : 163(100.2-230), 168(121-219.2), 168(110.2-222.6) ng/dl ,Total Thyroxine (T4) : 8.4(4.05-16.64) , 10.2(4.09-18.7), 11.2(3.8-16.7) µg/dl and Thyroid Stimulating Hormone (TSH):2.52(1.6-7.9) 3.01(1.28-7.6) 3(1.5-8.4) µIU/ml

Conclusions: The trimester-specific reference intervals and median for thyroid hormones during normal pregnancy have been established for pregnant South Indian women in Andhra Pradesh by full term follow-up during pregnancy using 2.5th and 97.5th percentiles and median.

Keywords: Median, Pregnant women, Reference intervals, Thyroid hormones, Trimester specific

INTRODUCTION

Physiological changes of pregnancy cause the thyroid gland to increase production of thyroid hormones by 40 to 100 percent to meet maternal and fetal needs. Total serum thyroxine (T4) increases sharply beginning between 6 and

9 weeks and reaches a plateau at 18 weeks. Free serum T4 levels rise slightly and peak along with hCG levels, and then they return to normal. The rise in total triiodothyronine (T3) is more pronounced up to 18 weeks, and thereafter, it plateaus. Thyroid-releasing hormone (TRH) levels are not increased during normal pregnancy, but this neurotransmitter does cross the placenta and may

serve to stimulate the fetal pituitary to secrete thyrotropin. Interestingly, the secretion of T4 and T3 is not similar for all pregnant women. Normal suppression of TSH during pregnancy may lead to a misdiagnosis of subclinical hyperthyroidism.¹

The mother's thyroid gland ordinarily enlarges up to 50 percent during pregnancy and increases its production of thyroxine a corresponding amount. The increased thyroxine production is caused at least partly by a thyrotropic effect of human chorionic gonadotropin secreted by the placenta and by small quantities of a specific thyroid-stimulating hormone, human chorionic thyrotropin, also secreted by the placenta.²

During pregnancy, the thyroid gland increases in size by 10% in iodine replete countries but by 20% to 40% in areas of iodine deficiency. Production of the thyroid hormones, thyroxine (T4), and triiodothyronine (T3), increases by nearly 50%, in conjunction with a separate 50% increase in the daily iodine requirement. Placental human chorionic gonadotropin (hCG) stimulates thyroid hormone secretion, often decreasing maternal thyrotropin (TSH) concentrations, especially in early pregnancy. But while such transiently suppressed maternal TSH concentrations are often observed and deemed safe, defining the upper reference limit for serum TSH in this population has remained controversial mild hyperthyroidism appears safe for the mother and fetus, moderate to severe hyperthyroidism can prove dangerous. Many have suggested universally valuating thyroid function in all women either before or during pregnancy.³

The range of thyrotropin (TSH), under the impact of placental human chorionic gonadotropin (hCG), is decreased throughout pregnancy with the lower normal TSH level in the first trimester being poorly defined and an upper limit of 2.5 mIU/L. Only recently has a TSH of 2.5 mIU/L been accepted as the upper limit of normal for TSH in the first trimester. Although it is well accepted that overt hypothyroidism and overt hyperthyroidism have a deleterious impact on pregnancy, studies are now focusing on the potential impact of subclinical hypothyroidism and subclinical hyperthyroidism on maternal and fetal health.⁴ It has been proven that maternal thyroid disorders influence the outcome of mother and fetus, during and also after pregnancy. Maternal hypothyroidism is the most frequent thyroid disorder in pregnancy and is associated with fetal loss, placental abruptions, preeclampsia, preterm delivery, and reduced intellectual function in the offspring.⁵⁻⁹

Overt hyperthyroidism complicates pregnancy by fetal loss, fetal growth restriction, preeclampsia, and preterm delivery. Mild or subclinical hyperthyroidism is seen in 1.7% of pregnancies and is not associated with adverse outcomes.¹⁰ Several studies from different regions of the world are available.¹¹⁻¹⁴ But very few studies till now has presented the trimester-specific thyroid function values in Indian women.¹⁵⁻¹⁸

The use of isotope dilution-LC/MS/MS for measuring T4 in the dialysate from equilibrium dialysis of serum is helpful to obtain a gold-standard reference measurement procedure for serum FT.¹⁹ This assay technology, unfortunately, is currently not widely available due to high instrument and operating costs. As most of the obstetricians are estimating the TSH, total T3 and T4 routinely and free T3 and T4 only when earlier values are abnormal.

In some of the studies subjects are not followed up in all three trimesters and reference values arrived based on the different subjects available in that trimester. Because of the current limited availability of reference intervals for thyroid function tests TSH and specifically total T3 and T4 in pregnant Indian women, author decided to evaluate this in o study for more accurate and appropriate interpretation of thyroid hormone levels in pregnant women.

The objective of this study was,

- To estimate and establish the normal reference range for Thyroid-Stimulating Hormone (TSH) during each trimester in normal pregnancy.
- To estimate and establish the normal reference range for total Triiodothyronine (T3) during each trimester in normal pregnancy.
- To estimate and establish the normal reference range for total Thyroxine (T4) during each trimester in normal pregnancy.

METHODS

A longitudinal study was conducted at obstetric clinic, Kakinada city, Andhra Pradesh over a period of 18 months from September 2017 to February 2019. Obstetric clinic instead of General hospital was selected, where it is very difficult for close follow-up of subjects. The total number of normal pregnancy subjects included in this study was 126. Thyroid hormones estimation was done by Competitive electrochemiluminescence (T3 and T4) and Sandwich electrochemiluminescence (TSH) at Thyorocare Laboratory using Advia Centaur [Siemens] analyzer. Only 47 subjects were having all three trimester thyroid hormone levels estimated during each trimester and were followed up to full term.

Inclusion criteria

- Subjects in the age group of 18-30 years
- Subjects who were willing to participate in the study and ready to give written consent for the same
- Subjects with normal singleton pregnancy
- Subjects who were followed up from conception to till full term.

Exclusion criteria

- Subjects with known thyroid disorders.
- Subjects who were on irregular follow up.

- Subjects with complicated pregnancies like pregnancy induced hypertension, hyperemesis, diabetes mellitus, heart diseases, and any other endocrine disorders.
- Subjects with multiple pregnancies.
- Subjects with history of liver dysfunction.
- Subjects with history of drug intake affecting thyroid function.
- Subjects with suffering from any chronic illnesses.

Trimester-specific visits were planned as follows:

- First trimester of pregnancy: 6-8 weeks.
- Second trimester of pregnancy: 16-18 weeks.
- Third trimester of pregnancy: 32-34 weeks.

Statistical Analysis

Data were entered and analyzed by using SPSS V22. Shapiro-Wilk test was applied to find normality. Data were not followed normality. Median with 2.5 and 97.5

percentiles were calculated. Friedman test was applied to find significance among three trimesters.

Wilcoxon signed rank test was applied to find significance between two trimesters, $p < 0.05$ was considered as statistically significant.

RESULTS

The total number of normal pregnancy subjects included in this study was 126. Out of 126 subjects applying the exclusion and inclusion criteria only 47 subjects were having all the three trimester thyroid hormone levels estimated during each trimester and were followed up to full term (Figure 1). Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) are not following the normal distribution curve. Only Triiodothyronine (T3) is following the normal distribution curve. As all the thyroid hormones were not following the normal distribution curve, percentiles were calculated for Thyroid hormones Triiodothyronine (T3), Thyroxine (T4) and Thyroid Stimulating Hormone (TSH).

Table 1: The trimester specific thyroid hormones values in percentiles and comparison of median thyroid hormones among three trimesters.

Hormone	IQR											
	5	10	25	50	75	90	95		1 vs 2	1 vs 3	2 vs 3	
T3 1 st trimester	121.4	129.6	138	163	182	202.6	206	44				
T3 2 nd trimester	121	128	142	168	178	202.8	215.2	36	<0.001	0.05	0.08	0.26
T3 3 rd trimester	119	120	144	168	180	199.8	219	36				
T4 1 st trimester	4.5	5	6.2	8.4	12.7	15	16.4	6.5				
T4 2 nd trimester	4.3	4.3	6	10.2	13.1	14.5	18.5	7.1	0.01	0.04	0.03	0.29
T4 3 rd trimester	4.1	4.4	6.9	11.2	12.7	16.2	16.5	5.8				
TSH 1 st trimester	1.8	2	2.2	2.5	3.5	4	7.1	1.3				
TSH 2 nd trimester	1.4	1.8	2.2	3	3.3	5.6	6.1	1.1	0.99	-	-	-
TSH 3 rd trimester	1.6	1.8	2.4	3	3.4	4.3	6.3	1				

From (Table 1): T3: Median T3 at 1st trimester was 163 ng/dl with IQR 44 ng/dl, at 2nd trimester was 168 ng/dl with IQR 36 ng/dl and at 3rd trimester 168 ng/dl with IQR 36 ng/dl. Median T3 among three trimesters was showing statistical significance but when comparing between two trimesters, only first and second trimester of Median T3 difference was showing statistical significance.

From (Table 1): T4: Median T4 at 1st trimester was 8.4 µg/dl with IQR 6.5 µg/dl, at 2nd trimester it was 10.2 µg/dl with IQR 7.1 µg/dl and at 3rd trimester it was 11.2 µg/dl with IQR 5.8 µg/dl. Median T4 among three trimesters was showing statistical significance but when comparing between two trimesters, except second and third trimester of Median T3 difference, remaining were showing statistical significance. From (Table 1):TSH: Median TSH at 1st trimester was 2.5 µIU/ml with IQR 1.3 µIU/ml, at 2nd

trimester it was 3 µIU/ml with IQR 1.1 µIU/ml and at 3rd trimester it was 3 µIU/ml with IQR 1 µIU/ml. Median T4 among three trimesters was showing no statistical significance.

From (Table 2): The thyroid hormone levels during first, second and third trimesters median with reference intervals are - Total Triiodothyronine (T3) : 163 (100.2 - 230), 168 (121 - 219.2), 168 (110.2 - 222.6) ng/dl, Total Thyroxine (T4) : 8.4 (4.05 - 16.64), 10.2 (4.09 - 18.7), 11.2 (3.8 - 16.7) µg/dl and Thyroid Stimulating Hormone (TSH) : 2.52 (1.6 - 7.9) 3.01 (1.28 - 7.6) 3 (1.5 - 8.4) µIU/ml. From (Table 2): The median with reference intervals during first trimester for thyroid-stimulating hormone (TSH) : 2.52 (1.6 - 7.9) µIU/ml, Total Triiodothyronine (T3) : 163 (100.2 - 230) ng/dl and Total Thyroxine (T4) : 8.4 (4.05 - 16.64) µg/dl.

Table 2: Reference intervals (2.5th and 97.5th percentiles) for thyroid hormone levels during each trimester.

Hormone	Percentiles			Median with reference intervals
	2.5	50	97.5	
T3 1 st trimester	100.2	163	230	163 (100.2 - 230) ng/dl
T3 2 nd trimester	121	168	219.2	168 (121 - 219.2) ng/dl
T3 3 rd trimester	110.2	168	222.6	168 (110.2 - 222.6) ng/dl
T4 1 st trimester	4.1	8.4	16.6	8.4 (4.05 - 16.64) µg/dl
T4 2 nd trimester	4.1	10.2	18.7	10.2 (4.09 - 18.7) µg/dl
T4 3 rd trimester	3.8	11.2	16.8	11.2 (3.8 - 16.7) µg/dl
TSH 1 st trimester	1.6	2.5	7.9	2.52 (1.6 - 7.9) µIU/ml
TSH 2 nd trimester	1.3	3	7.6	3.01 (1.28 - 7.6) µIU/ml
TSH 3 rd trimester	1.5	3	8.4	3 (1.5 - 8.4) µIU/ml

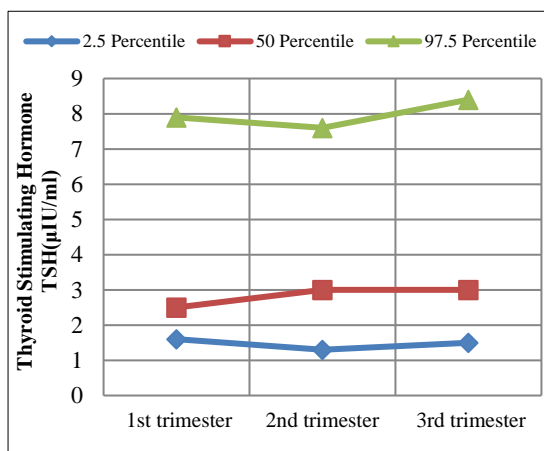


Figure 1: Thyroid stimulating hormone level during each trimester of normal pregnancy.

Triiodothyronine (T3) : 168 (110.2 - 222.6) ng/dl and Total Thyroxine (T4) : 11.2 (3.8 - 16.7) (Figure 2 and 3).

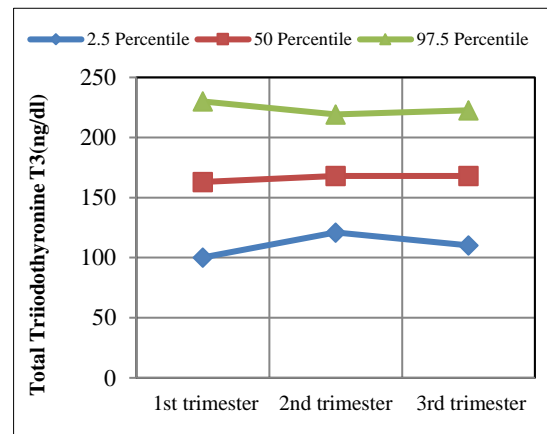


Figure 3: Total triiodothyroxine levels during each trimester of normal pregnancy.

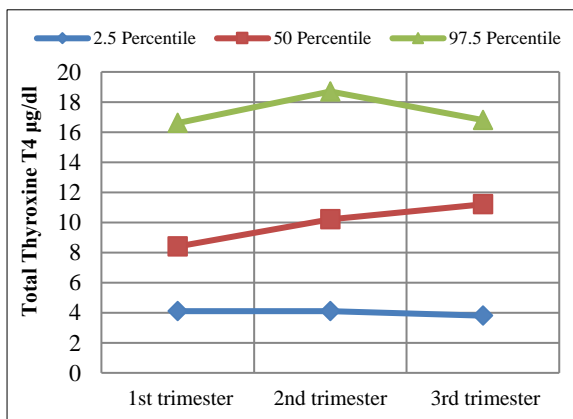


Figure 2: Total thyroxine levels during each trimester of normal pregnancy.

During second trimester for thyroid-stimulating hormone (TSH) : 3.01 (1.28 - 7.6) µIU/ml, Total Triiodothyronine (T3) : 168 (121 - 219.2) ng/dl and Total Thyroxine (T4) : 10.2 (4.09 - 18.7) µg/dl. In the third trimester for thyroid-stimulating hormone (TSH) : 3 (1.5 - 8.4) µIU/ml, Total

DISCUSSION

The present study provides reference intervals for thyroid hormone levels during each trimester in normal pregnancy. Thyroid hormones have great impact on fetal development and growth. The fetus has two potential sources of thyroid hormones - its own thyroid and the thyroid of its mother. Human fetuses acquire the ability to synthesize thyroid hormones at roughly 12 weeks of gestation. In hypothyroid woman, when pregnancy does occur, there is increased risk of intrauterine fetal death and gestational hypertension.^{20,21} Subclinical hypothyroidism is increasingly being recognized as a cause of developmental disease.²¹ As most of the obstetricians are estimating the TSH, total T3 and T4 routinely and free T3 and T4 only when earlier values are abnormal. Therefore, it is necessary to establish a reference range of thyroid hormones in particular total T3 and T4 for all the 3 trimesters of pregnancy separately.

In the study carried out by Kumar et al, in 2003 the Thyroid function tests in pregnancy, the Mean TSH levels were seen to rise progressively through the three trimesters of pregnancy from 1.20 microIU/ml in the first trimester to 2.12 microIU/ml in the second trimester and further to 3.30 microIU/ml in the third trimester of pregnancy.¹⁸ In this study the Median TSH levels were seen to rise progressively to second trimester of pregnancy from 2.52 microIU/ml in the first trimester to 3.01 microIU/ml in the second trimester and thereafter, it plateaus to 3 microIU/ml in the third trimester of pregnancy.

In the study carried out by Marwaha et al, in 2008 to establish reference range for thyroid hormones in normal pregnant Indian women.¹⁵ The TSH 5-95 Percentiles in Marwaha et al, study were (0.6-5, 0.44-5.78, 0.74-5.7 mIU/L) and in this study (1.8-7.1, 1.4-6.1, 1.6-6.3 µIU/ml). In another study carried out by Tarun Sekhri et al, in between June 2007 and June 2010, the TSH 2.5-97.5.¹⁶ Percentiles were 0.09-6.65, 0.51-6.66, 0.91-4.86 µIU/mL, and in this study 1.6-7.9, 1.3-7.6, 1.5-8.4 µIU/ml. Recent study carried out by Mankar et al, in 2014 the TSH 5th and 95th Percentiles Mankar et al, 0.24-4.17, 0.78-5.67, 0.47-5.78 µIU/ml in this study 1.8-7.1, 1.4-6.1, 1.6-6.3 µIU/ml.¹⁷

The trimester specific reference range in Iranian study was found to be: In first, second, and third trimester TSH (0.2-3.9, 0.5-4.1, and 0.4-1) in this study 1.8-7.1, 1.4-6.1, 1.6-6.3 µIU/ml. The average gestational age in this study in first trimester- 7th week, second trimester- 17th week, and third trimester -33rd week and, the TSH 2.5-97.5 Percentiles were 1.6-7.9, 1.3-7.6, 1.5-8.4 µIU/ml. The trimester specific reference range in American study at gestational age of 7th week 0.14, 1.21, 5.09 µIU/ml, 17th week 0.02, 0.98, 3.32 µIU/ml 33rd week 0.31, 1.20, 5.25 µIU/ml.²²

The reference values of thyroid hormones TSH in present study matches with other four Indian and western studies. The only difference was the lower limit and upper limit values are higher.

In the Iranian study carried out by Mehran L et al, in 2012 to establish reference range for thyroid hormones in normal pregnant Iranian women.²³ The values are TSH (mU/L) First trimester 0.2, 1.5, 3.9, Second trimester 0.5, 1.8, 4.1, Third trimester 0.6, 1.8, 4.1. TT3 (ng/dL) First trimester 138, 190, 278, Second trimester 155, 221, 328, Third trimester 137, 228, 324. TT4 (µg/dL) First trimester 8.2, 12.9, 18.5, Second trimester 10.1, 14.0, 20.6, Third trimester 9.0, 13.4, 19.4. Whereas in this study TSH (µIU/ml) 1st trimester 1.8, 2.5, 7.1, 2nd trimester 1.4, 3.0, 6.1, 3rd trimester 1.6, 3.0, 6.3. TT3 (ng/dl) 1st trimester 121.4, 163.0, 206.0, 2nd trimester 121.0, 168.0, 215.2, 3rd trimester 119.0, 168.0, 219.0. TT4 (µg/dl) 1st trimester 4.5, 8.4, 16.4, 2nd trimester 4.3, 10.2, 18.5, 3rd trimester 4.1, 11.2, 16.5.

The results are similar but with little difference in the values and following same pattern throughout the pregnancy. The major difference between four Indian, western studies except Iranian study and this study is that they have estimated free T3 and free while author have done total T3 and total T4.

CONCLUSION

The trimester-specific reference intervals and median for thyroid hormones during normal pregnancy have been established for pregnant South Indian women in Andhra Pradesh by full term follow-up during pregnancy using 2.5th and 97.5th percentiles and median. The present study reemphasises establishment of trimester-specific reference intervals for thyroid hormones during normal pregnancy as it varies from place to place.

Recommendations

There is a necessity of establishment of geographic specific reference values for that population.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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