# Establishing Trimester-Specific Reference Ranges for Thyroid Hormones in Indian Women with Normal Pregnancy: New Light through Old Window

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## ABSTRACT

**Introduction:** Assessment of thyroid function during pregnancy is important for assessing maternal and foetal well being. However, the complex physiological alterations occurring during normal pregnancy cause thyroid hormone levels to change. Hence, the interpretation of the thyroid profile becomes difficult in pregnancy if normal reference ranges are not defined. Study objective was to determine trimester specific reference ranges for thyroid hormone in normal pregnancy.

**Material and methods:** Serum sample was collected from 194 females in various trimester of normal intrauterine single pregnancy and total T3, total T4 and TSH was determined. The results obtained were then analysed to determine gestation specific thyroid hormone levels.

**Result:** The normal ranges of thyroid hormone in first, second and third trimesters during normal pregnancy in our study were: total T3 (83.9-196.6, 86.1-217.4, 79.9-186 ng/dl), total T4 (4.4-11.5, 4.9-12.2, 5.1-13.2 µg/dl) and TSH (0.1-2.7, 0.4-3.3, 0.5-3.8 IU/ml) respectively.

**Conclusion:** The levels of thyroid hormones in pregnancy not only show characteristic changes from non pregnant state but also vary with each trimester. Hence, trimester specific reference ranges for thyroid hormone need to be defined to ensure correct interpretation of these tests.


**Keywords:** Trimester, Thyroid Hormones, Normal Pregnancy

## INTRODUCTION

The increased metabolic demands during pregnancy set off a myriad important but reversible changes in the body.[1,2] A significant of these changes is effect on thyroid functions. In normal pregnancy there is increase in plasma thyroid binding globulin (TBG) concentration due to estrogen stimulated increased synthesis as well as decreased clearance of protein, increase in pool of extrathyroidal T4 distribution and increased deiodination of thyroid hormone in developing placenta.[1-4] These changes are in response to increased demand of thyroid hormone by developing foetus which in first two trimesters cannot synthesize sufficient thyroid hormone and is hence dependent on the maternal source of thyroid hormone. This is aided by Human chorionic gonadotrophin (hCG) which has a weak stimulating action on thyroid.[1]

All these factors are responsible for increased demand of iodine during pregnancy.

During first trimester of pregnancy, due to action of hCG, there is increase in the T3 and T4 concentration leading to suppression of TSH.[1] A steady state is achieved in pregnancy by mid gestation as the total T3 and T4 in the body fall and TSH gradually rises.[1]

The importance of thyroid hormone in fertility as well as foetal viability and development is well known.[2] Thyroid dysfunction during pregnancy is related to various complications. Hypothyroidism during pregnancy is said to be associated with maternal complications like anemia, post partum hemorrhage, pre-eclampsia and foetal complications like prematurity, low birth weight, congenital malformation, perinatal death, neurodevelopmental delay and congenital hypothyroidism. Hyperthyroidism during pregnancy, which is mostly due to Grave's disease can lead to adverse pregnancy outcomes and fetal growth retardation.[3] Hence several studies have been conducted across the globe to determine the normal reference range of thyroid hormones in pregnant females. However, these values vary with ethnicity, geographical location and method used for estimation.[6] Therefore, gestation-wise reference ranges specific for a particular area should be determined by each laboratory for a particular type of methodology being used.[6]

In this study we aimed at establishing gestation wise ranges for total T3, total T4 and TSH by chemiluminescent immunoassay in normal pregnant females with single intrauterine pregnancy in our laboratory at a tertiary hospital.

## MATERIAL AND METHODS

### Subjects

A cross-sectional observational study was conducted on 194 pregnant women attending antenatal clinic in a hospital

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located in northern India. The inclusion criteria were single intrauterine pregnancy and subjects consuming iodide salt. Exclusion criteria for the study were hyperemesis gravidarum, trophoblastic disease, multiple pregnancy, pregnancy induced hypertension, diabetes or any metabolic disease, history of pre-existing thyroid disease, infertility treatment and bad obstetric history.

Samples were randomly collected from pregnant females during the first (66 samples), the second (66 samples), and the third (62 samples) trimesters. The age of the pregnant females included in the study ranged from 19 to 34 years.

**Blood sampling and hormones analyses**

Blood sample was collected between 0800- 0900 h in the morning from the study group and the serum was separated. Analysis of serum levels for thyroid stimulating hormone (TSH), total thyroxin (TT4), and total triiodothyronine (TT3) was done using commercially available chemiluminescent immunoassay kits. Cases with TSH ≥4 IU/L were further tested for anti TPO antibodies and if found positive were excluded from the study.

## STATISTICAL ANALYSIS

The data was statistically analysed to obtain mean with standard deviation (SD) values. The 2SD value was then used to calculate the range.

## RESULT

The results obtained for total T3, total T4 and TSH in first, second and third trimester in pregnant females are as shown in table 1. It was noted that the total T3 and total T4 increased steadily in first two trimesters after which T3 started declining while T4 remained elevated (Fig.1,2). On the other hand

| **Total T3 (ng/dl)** | | | |
|---|---|---|---|
| **Subjects** | **Mean** | **SD** | **Range** |
| First trimester (N=66) | 140 | 28.1 | 83.9-196.6 |
| Second trimester (N=66) | 151.8 | 32.9 | 86.1-217.4 |
| Third trimester (N=62) | 133 | 26.5 | 79.9-186 |
| **Total T4 (ug/dl)** | | | |
| **Subjects** | **Mean** | **SD** | **Range** |
| First trimester (N=66) | 7.9 | 1.7 | 4.4-11.5 |
| Second trimester (N=66) | 8.5 | 1.8 | 4.9-12.2 |
| Third trimester (N=62) | 9.1 | 2.04 | 5.1-13.2 |
| **TSH (IU/ml)** | | | |
| **Subjects** | **Mean** | **SD** | **Range** |
| First trimester (N=66) | 1.4 | 0.7 | 0.1-2.7 |
| Second trimester (N=66) | 1.8 | 0.7 | 0.4-3.3 |
| Third trimester (N=62) | 2.1 | 0.8 | 0.5-3.8 |

**Table-1:** Trimester specific ranges for thyroid function test in pregnant females.

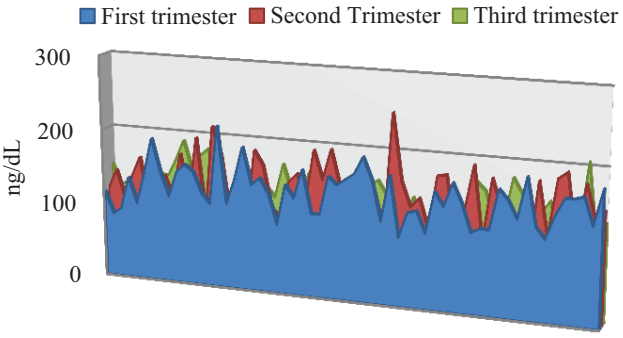


**Figure-1:** Serum total T3 levels in the three trimesters

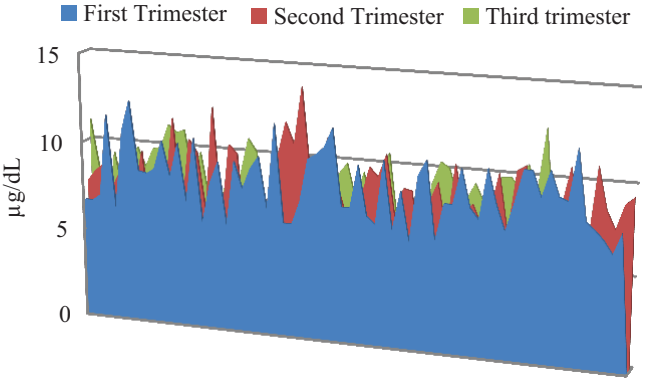


**Figure-2:** Serum total T4 levels in the three trimesters

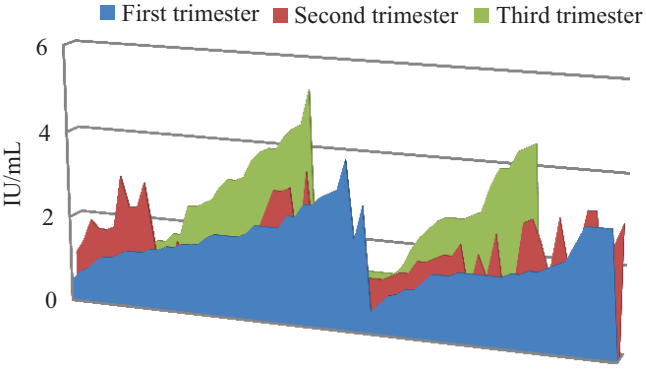


**Figure-3:** Serum TSH levels in the three trimesters

serum TSH decreased in first trimester and gradually started rising in second trimester going on to highest levels in third trimester (Fig. 3). The mean value for T3 in first trimester was 140 ng/dl which gradually rose to 151.8 ng/dl in second trimester and then decreased to 133 ng/dl in third trimester. The mean value of serum T4 steadily increased from 7.9 µg/dl in first trimester, 8.5 µg/dl in second trimester to 9.1 µg/dl in third trimester. It was noted that TSH decreased in first trimester with range of 0.1 to 2.7 IU/ml (mean 1.4 IU/ml) in first trimester rising to mean value of 1.8 IU/L and 2.1 IU/L in second and third trimester respectively.

## DISCUSSION

There is a complex change in thyroid profile during pregnancy. During the first trimester of pregnancy hCG has stimulating effect on thyroid gland leading to increase in T3 and T4 along with corresponding fall in TSH levels. Other factors influencing thyroid profile in pregnant females are the estrogen stimulated increase in TBG, increase in

extrathyroidal pool of distribution of T4 along with increased deiodination of thyroid hormone in the placenta. In the first two trimesters of pregnancy, the thyroid –pituitary axis of the foetus is not mature and hence it is completely dependent on the maternal supply of thyroid hormones for growth and viability. Maternal hypothyroidism may lead to preterm delivery, foetal loss or low intelligence in the child. Hence, trimester-wise determination of reference range of thyroid hormones in pregnant females is of vital importance for screening and correct interpretation of reports.

In our study we analysed total T3, total T4 and TSH in pregnant females in various trimesters. Estimation of free T3 and free T4 has been recommended by several studies. This is because immunoassays for total T3 and T4 have been found to have lack of specificity by various studies.[7,8] This is mainly due to of presence of iodothyronine-binding auto-antibodies in the maternal serum that interfere in the T3 and T4 assay.[9,10] However, free T3 and T4 assays are costlier and more difficult to analyse in picomole range due to interference by high levels of total hormone in pregnant females.[11,12] Moreover, various studies have revealed that free T4 analysis is susceptible to interfering factors like thyroid binding globulin and albumin. These interfering factors not only reflect as inter-assay but also inter-individual differences in the results.[18,19] Hence total T3 and total T4 estimation may provide a cheaper and simpler adjunct to serum TSH levels estimation during pregnancy.

Serum TSH comprises a major screening tool for thyroid function in pregnant females. In early pregnancy (especially before 10 weeks of gestation) TSH is suppressed due to presence of hCG and hence the values of serum T3 and T4 (free or total) become important for assessment of thyroid function.[13,14]

In a study conducted by Marwah et al on 541 healthy pregnant females in an Indian primary care level obstetric department, the range for TSH in first, second and third trimester of pregnancy was found to be 0.6-5.0, 0.44-5.78 and 0.74-5.7 IU/ml respectively.[15] In another study conducted by Kumar *et al* on 124 apparently healthy pregnant females it was found that the mean total T3 increased during second trimester and then decreased in third trimester.[16] Similar finding was obtained in our study. However, total T4 level was found to rise in second and then decline in third trimester by Kumar *et al* while in our study it increased progressively and peaked in third trimester.[16] This difference may be due to difference in sample size in the two studies.

The American thyroid association recommends following trimester-specific ranges for TSH for laboratories where reference ranges are not available: 0.1-2.5, 0.2-3.0 and 0.3-3.0 mIU/L for first, second and third trimester respectively.[17] These cut offs are lower than reference ranges for normal non-pregnant females as was revealed in our study also.

## CONCLUSION

The effect of thyroid profile on foetal development is well known. Hence it is imperative to define reference ranges for thyroid profile in pregnant females for screening and detection of thyroid illness. In our study on 194 pregnant females we found that the normal ranges in first, second and third trimesters were: total T3 (83.9-196.6, 86.1-217.4, 79.9-186 ng/dl), total T4 (4.4-11.5, 4.9-12.2, 5.1-13.2 ug/dl) and TSH (0.1-2.7, 0.4-3.3, 0.5-3.8 IU/ml). The upper limit of normal for TSH in our study is <4 IU/L thus emphasising on need to revise the reference range for pregnant females to a value which is lower than that of normal non pregnant female. This would ensure a correct and more scientific interpretation of thyroid function screening tests in pregnant females.

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