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Trimester Specific Thyroid Profile Reference Ranges for Pregnant Women in South Indian Population

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ABSTRACT

Introduction:
It is crucial to measure thyroid function throughout pregnancy to determine the health of the mother and foetus. However, a woman's thyroid hormone levels alter during pregnancy due to complex physiological changes. If typical reference ranges are not established it becomes challenging to interpret the thyroid profile during pregnancy. The goal of the study was to identify reference levels for thyroid hormone in healthy pregnancy in particular to each trimester.

Aim and Objectives:
To study the trimester – specific thyroid profile hormones in pregnant women.
To estimate the level of thyroid hormones ranges in the first, second and third trimester pregnant women.
To establish trimester – specific reference ranges for TSH, free T3 (FT3), and free T4 (FT4) in apparently healthy pregnant women and to compare with standard reference ranges.

Methodology:
This study was conducted in a tertiary care hospital at Puducherry with 270 pregnant women
Estimation of thyroid profile using Chemiluminescence immunoassay technique.

Result:
The normal ranges of thyroid hormone in first, second and third trimesters during normal pregnancy in our study were: total FT3 (2.27-2.79, 2.55-2.82, 2.73- 2.91pg/ml, total FT4 (1.53-2.73, 1.00-1.40, 1.07-1.20ng/dl) and total TSH (1.78-2.32, 2.01-2.56, 2.02-2.46µIU/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.

INTRODUCTION

Thyroid abnormalities are the second most frequent endocrine illnesses that women experience during their reproductive years. Women are more prone to thyroid problems during pregnancy. In order to safeguard the health of both mother and the unborn child, thyroid problem must be identified and treated before during pregnancy.(1) Infertility and pregnancy risk can both be negatively impacted by thyroid issues. Although gestational hypothyroidism is more common (2.5%) than pregnant hyperthyroidism (0.2%), both conditions can cause newborn and infant neurodevelopmental disorders as well as maternal obstetric issues.(2)

A significant risk to the pregnancy is not posed by subclinical hyperthyroidism. So, it's imperative that we maintain TSH levels within the standard reference range for each trimester. In order to guarantee that the foetus receives the right nutrition, the mother modifies a number of organ systems throughout pregnancy, including her hormonal and metabolic systems.(3) The thyroid gland adjusts by controlling thyroid hormones via the hypothalamus pituitary-thyroid axis during this process.(4) Particularly during the first trimester, when the foetus is entirely dependent on the mother's thyroid supply delivered through the placenta, thyroid hormones are crucial for the fetus's proper growth.(5)

During pregnancy, thyroid gland dysfunction is frequently experienced and is linked to obstetric problems. Maternal hypothyroidism is the thyroid condition that affects pregnant women most frequently.(6) Preeclampsia, intrauterine growth restriction, and other pregnancy problems are linked to uncontrolled thyrotoxicosis during pregnancy. Cardiac failure can come from increased thyroid secretion brought on by the demands of pregnancy, which is exacerbated by the hyperactive circulation of pregnancy.7 In the past few years, there has been debate concerning the definition and modification of normative data for TSH values in pregnancy. TSH threshold values for various publications, suggestions, and guidelines in the literature vary.(7)

Increased basal metabolic rate, increased thyroid hormone secretion due to activity of human chorionic gonadotrophin (HCG) and human chorionic thyrotropin (HCT), which share a similar molecular structure, as well as receptor cross-reactivity with TSH are all effects of pregnancy's increased metabolic demand. When compared to TSH, HCG has a 1/4000th of the efficacy to stimulate thyroid function.(8) During pregnancy, there are significant changes in circulating maternal steroid hormones and thyroid steroid binding globulin (TBG) concentrations. It is believed that pregnancy causes an increase in total thyroxine (TT4) and total triiodothyronine (TT3) concentrations. In pregnancy, TBG concentrations increase between weeks 16 and 20. Pregnancy frequently causes slight declines in serum transthyretin and albumin levels in addition to the 2- to 3- fold increase in blood TBG.(9)

In the second and third trimesters, free T3 (FT3) and free T4 (FT4) levels are slightly lower. Thyroid-stimulating hormone (TSH) levels are low-normal in the first trimester, but they return to normal in the second.2 Hence, purpose of this study is to establish trimester- specific thyroid profile reference ranges for TSH, free T3 (FT3) and FT4 in apparently healthy pregnant women.

Aim

- To study the trimester – specific thyroid profile values of thyroid hormones in pregnant women.
- To estimate the levels of thyroid hormones ranges in the first, second, third pregnant women.
- To establish trimester-specific reference ranges for TSH, free T3 (FT3), and FT4 in apparently healthy pregnant women and compare with standard reference ranges.

STUDY AREA

This cohort study was conducted in a tertiary care hospital at Puducherry, approved by the Institutional Research Council (IRC) and Institutional Human Ethical Committee (IHEC) (MGMCRI/2022/01/IHEC/45).

Pregnant healthy women between the ages 20 to 40 years, attending the Obstetrics and Gynecology department were included in the study. Sample size was 270, which were equally divided into first, second and third trimester.

MATERIALS AND METHOD

Collection of blood sample

After obtaining informed consent from the study participant and after taking aseptic precautions venous blood samples were collected from antecubital vein. Blood samples were centrifuged at 3000 rpm/min and analyzed for biochemical parameters (FT3, FT4 and TSH). The left over serum samples will be stored at -20°C until the target sample size is achieved.

PARAMETERS STUDIED

Anthropometric Parameter:

Age, Weight, Height and BMI of the participants were obtained.

Biochemical Parameter:

Biochemical parameters TSH, FT3, and FT4 were estimated by electrochemiluminescence (ECL) technology (COBAS E411)

STATISTICAL ANALYSIS:

Data were entered and tabulated in Microsoft Excel. Data were processed using JASP statistical package version 0.17.1, from the University of Amsterdam.

RESULTS:

All the observations were recorded and expressed as Mean ± SD. A total number of 270 pregnant women were enrolled in this study.

Trimester-wise mean age and gestational age of the study patients were given in **table 1**. The average gestational age were 27.16 ± 3.79 (range 4-12 weeks), 26.9 ± 3.71 (range 16-24) and 27.07 ± 3.83 (range 28-36) at the first, second and third trimester, respectively

Table 1: Trimester-wise mean age and gestational age of the study patients

Descriptive – age					
Group	**N**	**Mean**	**SD**	**SE**	**Ranges**
Trimester 1	90	27.167	3.799	0.4	26.38-27.95
Trimester 2	90	26.944	3.707	0.391	26.17-27.71
Trimester 3	90	27.067	3.833	0.404	26.27-27.85

FT3, FT4, and TSH test values illustrated in figures (1 to 3);

Figure 1: Bar diagram for FT3

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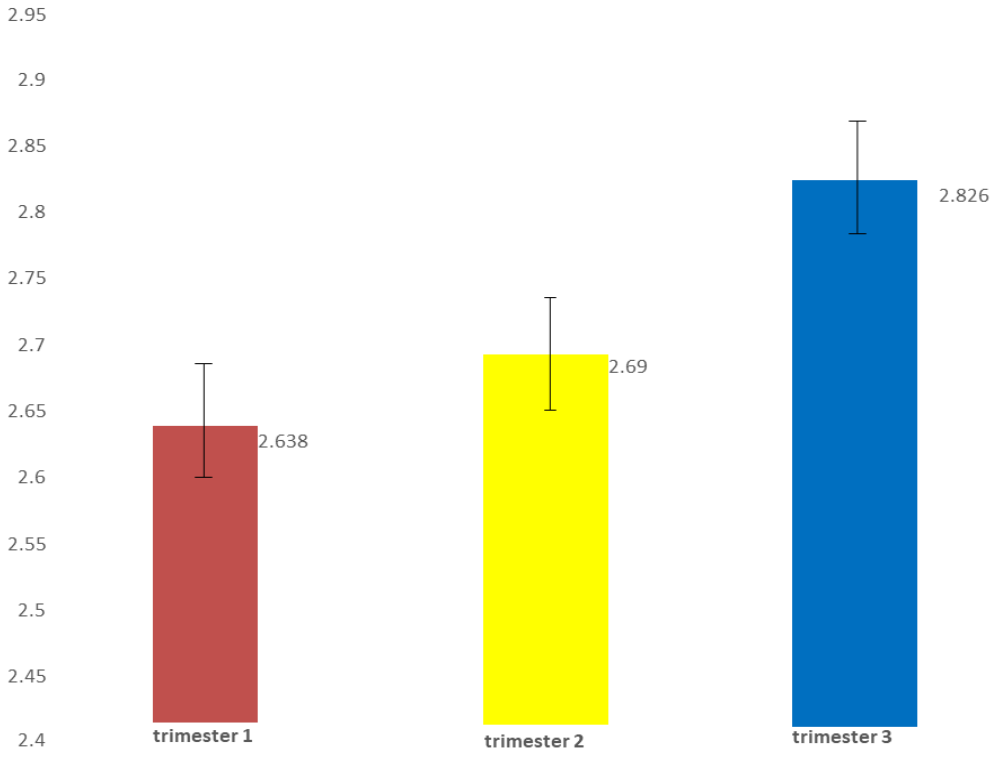


Figure 2: Bar Diagram for FT4

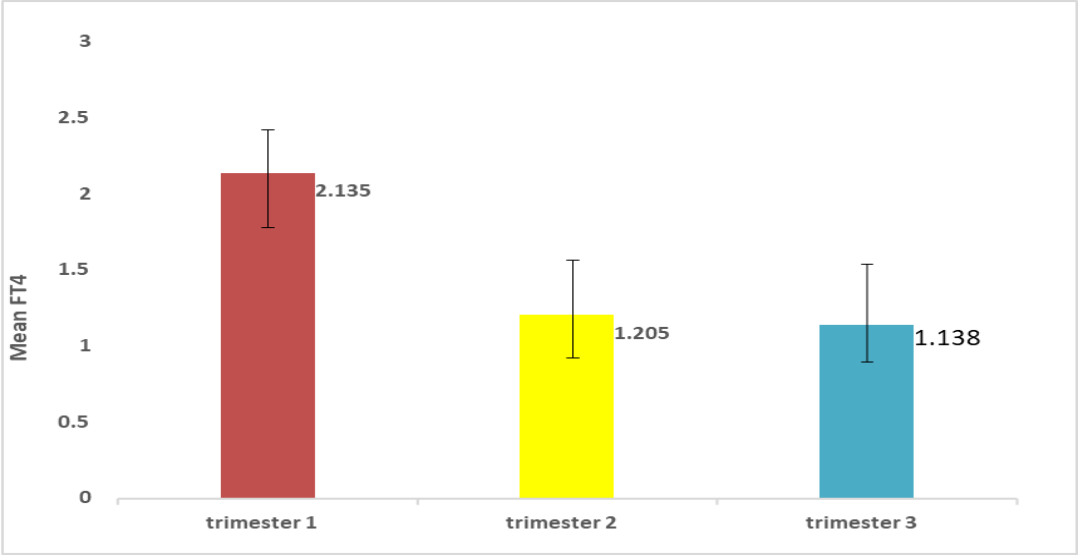
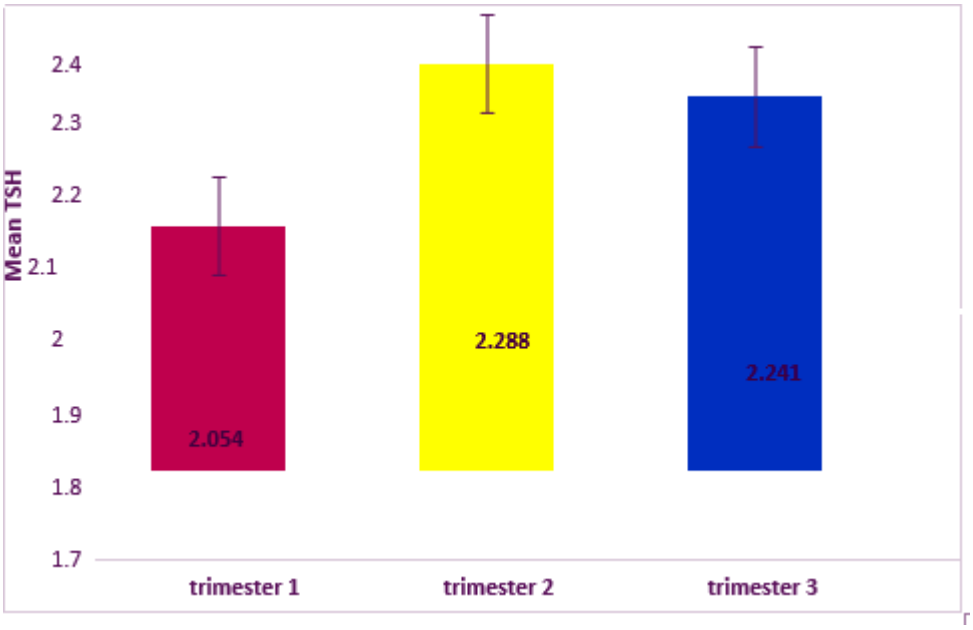


Figure 3: Bar diagram for TSH



DISCUSSION

Cotzias et al., in their study calculated clinically relevant gestation-specific reference intervals using appropriate statistical analytic techniques and common biochemical procedures. These can be applied to enhance thyroid disease management during pregnancy. They represent both the laboratory method utilized and our multiethnic, iodine-rich community. These findings will help clinicians understand how thyroid function changes during pregnancy and enable them to manage patients using gestation-specific reference ranges. (10)

Kulhari et al., showed that the thyroid gland is stimulated by hCG during the first trimester of pregnancy, which causes an increase in T3 and T4 levels and a corresponding decrease in TSH levels. The estrogen-stimulated increase in TBG, the rise in the extra thyroidal pool of T4 distribution, and the enhanced deiodination of thyroid hormone in the placenta are additional factors that affect the thyroid profile in pregnant women. Because the foetus thyroid-pituitary axis is still developing in the first two trimesters of pregnancy, it is entirely dependent on the mother's supply of thyroid hormones for growth and viability. Hypothyroidism in the mother can cause premature labour, foetal loss, or poor IQ in the offspring. Therefore, it is crucial for screening and accurate report interpretation that the reference range of thyroid hormones in pregnant females to be determined trimester by trimester.(11)

In our study, total T3, total T4, and TSH levels in pregnant women at various trimesters were investigated. According to numerous research it is advised to estimate free T3, free T4 and TSH. This is due to the fact that numerous studies have discovered a lack of specificity in immunoassays for total T3 and T4.(12) This is mostly caused by the maternal serum's presence of iodothyronine-binding autoantibodies, which obstruct the T3 and T4 test.(13) The trimester-wise values in the first, second and third trimesters were: FT3 (2.48-2.80, 2.55-2.82 and 2.73-2.91pg/ml), FT4 (1.53-2.73,1.00-1.40 and 1.07-1.20ng/dl) and TSH (1.78-2.32, 2.00-2.57 and 2.02-2.46µ IU/ml), respectively.

The thyroid function reference intervals vary significantly among various populations of pregnant women. Variations in the assays and population-specific elements like ethnicity and body mass index can be used to explain these discrepancies. Even minor subclinical variations in thyroid function have been linked to unfavorable pregnancy outcomes, such as low birth weight and pregnancy loss, which emphasizes the significance of using accurate reference intervals. Therefore, it is crucial that institutions determine their own pregnancy- specific reference intervals rather relying on a fixed universal cutoff concentration. Two percent to four percent of pregnant women experiences thyroid dysfunction. Infertility, intrauterine growth retardation, hypertensive disorders, preterm delivery, and lower IQ scores in children are all increased risks for both mothers and their offspring when there is maternal thyroid dysfunction. To ensure that the mother and foetus receive enough thyroid hormones T3 during pregnancy, significant changes in thyroid physiology take place. This is crucial in the early stages of pregnancy because the fetus depends heavily on the mother's supply of thyroid until it begins to produce significant amounts of thyroid at around 20 weeks of gestation. (14)

Due to the fetus's need for Thyroid, rising levels of thyroid-binding proteins (such as thyroxine -binding globulin), Thyroid production must rise. Human chorionic gonadotropin, a pregnancy hormone and a week agonist of the thyroid-stimulating hormone (TSH) receptor, plays a role in mediating this process, which necessitates a healthy thyroid gland and adequate dietary iodine availability. TSH and FT4 reference intervals differ from those in the non-pregnant state as a result of the rise in serum free thyroxine (FT4) concentrations and decline in TSH concentrations beginning around the eighth week of pregnancy.

It is crucial to establish reference intervals for normal thyroid function throughout pregnancy given these pregnancy-related changes in thyroid physiology and the complications linked to thyroid dysfunction. Finding women who might benefit from treatment and identifying them is essential.(14) Because of this, it is advised by the Endocrine Society, American Thyroid Association and European Thyroid Association's guidelines to calculate trimester-specific reference intervals for each center. Most institutions still rely on these fixed reference intervals even though center-specific reference intervals for numerous additional pregnancy cohorts have been published since the publications of these guidelines show significant variations in TSH cutoffs. This is especially important given that even subclinical thyroid dysfunction which is typically defined using population-based cutoffs- is linked to a higher risk of unfavorable outcomes for both the mother and the child. In light of the various factors that affect thyroid function reference intervals during pregnancy as well as the clinical ramifications linked to small variations in thyroid function, this study offers an insight on these intervals. Kurioka et al., 2005 showed that numerous studies on expectant mothers are available some of the cross-sectional while others are longitudinal within the same study group. They differ as well in terms of how thyroid

hormones are estimated through assay. The authors of one cross-sectional study found that as pregnancy progressed, there was a significant decrease in both FT3 and FT4 and an increase in TSH in the sample of 522 pregnant women from Japan who used ECL kits.(11,15) Price et al., 2001 showed that thyroid function was determined using immunoassay in a second longitudinal study, but only paired samples from the first and second trimesters of 20 pregnant Asian women were examined.(15) Kumar et al., 2003 showed that another study from India that used radioimmunoassay to evaluate 124 pregnant women found that TSH increased gradually with each trimester.(16) Panesar et al.,2001 discovered that, as pregnancy advanced, FT4 decreased while TSH increased from the first to the second trimester. Between the first and second trimesters, FT3 remained stable. Although there are few studies that focus on this topic, ethnic differences continue to be a concern. Panesar et al proved that during the second trimester of pregnancy, Asian women's TSH levels were lower than those of Caucasian women. They believe that Asian women are more likely to experience gestational thyrotoxicosis, despite the fact that we were unable to identify any cases of overt hyperthyroidism. Recent thyroid function research that was limited to the second trimester of pregnancy revealed that white people were more likely than Asians and Black people to have elevated TSH levels. (17)

CONCLUSION

In the present study, Establishment of trimester specific range was done in 270 pregnant women in the age group between 20 to 40 years from South Indian Population, TSH, FT3 and FT4 were estimated by Electro Chemiluminescent Technology. There was an increase in the mean TSH value from 1st to 2nd trimester but it was decrease in 3rd trimester so it was not statistically significant, there was an increase in the mean FT3 value from 1st, 2nd and 3rd trimester so it was not statistically significant and there was a decrease in the mean FT4 value from 1st, 2nd and 3rd trimester so it was statistically significant.

Establishment of reference ranges create awareness about trimester specific reference which is helpful for clinical correlation and help in early diagnosis of hypothyroidism and hyperthyroidism

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