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Trimester-Specific Reference Intervals for Thyroid Function Tests during Pregnancy: A Cross-Sectional Analysis

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ABSTRACT

BACKGROUND:

Pathological changes in maternal thyroid hormone (TH) levels during pregnancy can lead to adverse outcomes for both the mother and the baby. This underscores the significance of Thyroid Function Tests (TFTs) during pregnancy. However, the dynamic alterations in thyroid gland function and hormone levels throughout pregnancy warrant the establishment of trimester-specific reference intervals, distinct from those used for non-pregnant females.
Aim: This study was conducted in a teaching hospital in northern India to determine trimester-specific reference intervals for TFTs among pregnant women in the region.

MATERIALS & METHODS: This cross-sectional study was conducted at a tertiary care teaching hospital in northern India. A cohort of 600 pregnant women attending the Obstetrics Outpatient Department was considered. Among them, 145 healthy women (constituting 33.35% of the presented pregnant women) aged between 18 and 40, with uncomplicated singleton intrauterine pregnancies, who consumed iodised salt, and were in their first trimester, were included in the study. Women in the second trimester (100 participants, 16.7%) and third trimester (300 participants, 50%) were excluded. From the initial 200 first-trimester patients, individuals with a family history of thyroid disease (15%), abortion history (10%), goitre (0.5%), anti-thyroid peroxidase positivity, overt hypothyroidism (1%), hyperthyroidism, or cases of twin pregnancies (1%) were further excluded. Participants were monitored across successive trimesters to record observations and determine trimester-specific reference ranges.

RESULTS: Our study revealed a progressive decline in serum free T3 and serum free T4 levels during subsequent trimesters, accompanied by increased serum TSH levels. Notably, the reference values for pregnant women substantially differed from those of non-pregnant individuals.

CONCLUSION: Thyroid function testing protocols must be tailored to the unique needs of pregnant women, distinct from those of non-pregnant counterparts. Laboratories should exercise vigilance regarding reference ranges, assays, and screening guidelines to ensure optimal patient care.

KEYWORDS: Free thyroxine, pregnancy, thyroid function tests, trimester-specific reference intervals, physiological changes.

INTRODUCTION

Thyroid disease is the second most prevalent endocrine disorder affecting women of reproductive age. The repercussions of thyroid disorders extend to reproductive and pregnancy-related outcomes. While gestational hyperthyroidism is rare (0.2%), gestational hypothyroidism occurs more frequently (2.5%) and poses risks of neonatal neurodevelopmental deficits and maternal obstetric complications [1]. Notably, subclinical thyroid disorders can also manifest during pregnancy. However, diagnosed thyroid dysfunction, when managed, usually permits uneventful pregnancies. The intricate interplay of pregnancy-induced changes, compounded by obstetric conditions like hyperemesis gravidarum or gestational trophoblastic disease, can disturb thyroid function, influencing maternal-fetal thyroid hormone equilibrium. Consequently, establishing trimester-specific reference intervals for thyroid function tests assumes paramount importance [2].

Pregnancy incites complex shifts in maternal steroid hormone levels and thyroid-binding globulin (TBG) concentrations. Elevated TBG concentrations, influenced by estrogen-induced changes in glycosylation, contribute significantly to heightened TBG levels during pregnancy, alongside estrogen's stimulatory effects on TBG synthesis. Plasma clearance of TBG is diminished during pregnancy, augmenting TBG concentration. Concurrently, minor reductions in serum transthyretin and albumin are expected in pregnancy. At the same time, total thyroxine (TT4) and total triiodothyronine (TT3) levels elevate due to pregnancy-induced hypothyroidism and increased TBG, free T3 (FT3) and free T4 (FT4) levels slightly decline in the later trimesters. Thyroid-stimulating hormone (TSH) levels exhibit low-normal values initially, normalising by the second trimester [3, 4, 5].

Post-delivery, rapid reversion occurs, restoring pregestational TBG, T4, and T3 concentrations within 4 to 6 weeks. Detecting thyroid hormone abnormalities during pregnancy requires establishing normative ranges across trimesters, a necessity especially pronounced in iodine-deficient populations [6].
Both overt and subclinical maternal thyroid disorders associate with pregnancy complications, exerting short- and long-term impacts on mothers and offspring. Risks are elevated in women with euthyroid autoimmune thyroid disease, wherein hypothyroidism during pregnancy relates to gestational hypertension and low birth weight. Pregnant women on pre-pregnancy thyroxine therapy might necessitate dosage adjustments. Autoimmune thyroiditis correlates with higher spontaneous miscarriage rates. Elevated TSH levels increase the risk of very preterm delivery. Antithyroglobulin antibody (TgAb)-positive gravidas face heightened preterm delivery risk. Trimester-specific thyroid hormone and TSH ranges are crucial for appropriate management [2, 5, 6].

Hyperthyroidism, primarily from Graves' disease, occurs in around 0.2% of pregnant women, potentially impacting both mother and child. Management includes anti-thyroid drugs, and PTU usage is advised, accompanied by TSH receptor antibody measurement at 36 weeks gestation [7].

MATERIALS & METHODS

A cross-sectional cohort study was conducted in the Department of Pathology at a teaching hospital in northern India from March 2016 to February 2017. The aim was to establish trimester-specific reference intervals for thyroid function tests during pregnancy. A total of 600 pregnant women were screened at the Obstetrics Outpatient Department (OPD). Of these, 145 healthy women (33.35% of presented pregnant women in OPD), aged 18 to 40 years, with uncomplicated singleton intrauterine pregnancies, and who consumed iodised salt, were enrolled in the study during their first trimester.

Those in the second trimester (100 participants, 16.7%) and third trimester (300 participants, 50%) were excluded.

From the initial 200 first-trimester patients, individuals with a family history of thyroid disease (15%), history of abortion (10%), goitre (0.5%), anti-thyroid peroxidase (TPO) positivity, overt hypothyroidism (1%), hyperthyroidism, or twin pregnancy (1%) were further excluded. Detailed patient histories were obtained to accurately date pregnancies and identify any metabolic or thyroid disorders and bad obstetric history. General and systemic examinations were conducted to detect associated systemic illnesses.

The clinical history encompassed hypo or hyperthyroidism symptoms before, during, or after pregnancy, gland enlargement, repeated abortions, and any history of autoimmune disorders. Physical examinations included routine bedside assessments, recording of height, weight, calculation of body mass index (BMI), and thorough thyroid gland, eyes, and skin examinations.

Pathological investigations included the following:
1. Complete hemogram
2. Liver function tests (SGOT, SGPT, alkaline phosphatase, bilirubin)
3. Renal function tests (serum creatinine, blood urea)
4. Urine analysis (routine and microscopy)
5. Oral glucose tolerance test
6. Serum calcium and phosphorus levels

Special investigations were conducted as follows:
- 1st Trimester: TSH, FT4, Anti TPO Antibodies
- 2nd Trimester: TSH, FT4
- 3rd Trimester: TSH, FT4

Participants were included in the study during the first trimester and were followed through their second and third trimesters. Informed consent was obtained from participants at each visit, and 10 ml venous blood samples were collected in fasting conditions. Serum was separated through centrifugation and stored at -20°C. Highly sensitive methods, specifically Electro Chemi Luminescence Immuno-Assay (ECLIA) on the Roche Elecsys 1010 immunoassay analyser, were employed for estimating hormonal levels, including triiodothyronine (FT3), thyroxine (FT4), thyroid stimulating hormone (TSH), and thyroid autoantibodies.

Reference range: Manufacturer's literature (Roche) non-pregnant women.

TSH	0.3 – 4.2 µ IU/mL
T3	12-22 pmol/L
T4	2.8- 7.1 pmol/L
TPO antibodies	34 IU/ml as TPO positive

RESULTS

In this study, a total of 145 apparently healthy pregnant females with known last menstrual periods and no known history of thyroid or any metabolic disorders, registered in the 1st trimester of the pregnancy in a teaching hospital were studied.
The serum free Tri iodo thyroxine (FT3), free Thyroxine (FT4), Thyroid Stimulating Hormone (TSH) levels were recorded in each trimester. The thyroid peroxidase antibodies (TPO-Ab) were also estimated in the 1st trimester.

Table 1 shows the distribution of the pregnant females according to age.

Table 1: Age-wise Distribution of females.

Age Group	No. of Case
15-20	18
21-30	123
>31	04
Total	145

The age of the subjects under study ranged from 19 years and 35 years. (Mean=24.2 years +/- 3.71(2standard deviation), Median= 23 years). Out of 145 patients 12.4% of cases were in the age group of 15-20 years followed by 84.8% in the age group of 21-30 years, and 2.7% from the age group of >31 years of age. The weight of the subjects ranged from 47 kgs to 66 kgs. The mean weight in kilogram was 54.97 +/- 6.52 (2 standard deviations). The mean height of the subjects in centimetre was 154.07 +/- 7.18 (2 standard deviation).

The mean serum calcium (mg%) of 145 subjects under study was 8.72 +/- 0.71 (2 standard deviation) followed by mean value for level of Alkaline phosphatase (IU/L) in these subjects was 217.6 +/- 41.6 (2 standard deviation).

In the 1st trimester, the mean haemoglobin (Hb) was 10.6 +/- 1.01 gm% (2 standard deviations). The range of Hb was from 8.7-12.5 gm%. According to ICMR definition the subject were classified as having mild, moderate and severe anaemia. Mild- 8.1-10.0 gm%, moderate - 5.1-8.0 gm% and severe anaemia with Hb ≤5 gm%. Out of 145 subjects 17.24% were found to have mild anaemia in the 1st trimester.

The patients with impaired glucose tolerance and other metabolic disorder were excluded from the study. The mean carbohydrate Gestational Intolerance (GCI) was with 50 gm glucose the 145 subjects under study was estimated as 101.4 +/- 11.7 mg% (2 standard deviation) the range was from 87-121 mg%.

The mean of Serum Creatinine 1.0 +/- 0.28 (2 Standard Deviation) and the range were 0.3 – 1.4 followed by blood urea mean 29.5 +/- 8.9 (2 Standard deviation) and the range was from 1-54 and the mean of total bilirubin was 0.9 +/- 0.3 (2 Standard deviation) and the range was from 0.1-1.3.

The mean of SGOT 24.1 +/- 6.4 (2 Standard Deviation) and the range from 10-36 followed by mean of SGPT 30.6 +/- 9.3 (2 Standard Deviation) and the range from 10- 47 were observed in the 1st trimester of females.

The mean value of free T3 (pmol/L) of the 145 pregnant subjects in first second and third trimested is shown in table 2.

Table 2: Variations in the level of free T3 (pmol/L) (N=145)

	1st Trimester	2nd Trimester	3rd Trimester
Mean	5.181	5.246	5.246
Standard Deviation	1.264	1.111	1.080
Min.	2.9	2.8	3.1
Max.	6.9	6.4	6.9

Multivariate repeated measurement analysis using Wilk's Lambda methods [table 3] showed that this decline in values of free T3 through the three trimesters is statically significant with p value <.001

Table 3: Multivariate repeated measurement analysis of free T3

Trimester	Estimated mean	Std. error	95% confidence interval	
			Upper Limit	Lower Limit
1st	5.181	0.105	5.1334	4.7344
2nd	5.246	0.092	5.4279	5.0004
3rd	5.246	0.089	5.4227	5.0748

Table 4: Variation in the level of free T4 (pmol/L) trimester wise (N=145)

	1st Trimester	2nd Trimester	3rd Trimester
Mean	16.4	15.8	15.1
Standard Deviation	2.539	2.365	2.228
Min.	12.8	12.4	12.2
Max.	21.9	20.4	20.1

The mean value of free T4 of the 145 pregnant subjects was found to be 16.4 +/- 2.53 (2 standard deviation) in the first trimester, subsequently the value slightly decrease to 15.8 +/- 2.36 (2 standard deviations) in the second trimester and 15.1 +/- 2.28 (2 standard deviation) (Table 4).

Table 5: Multivariate repeated measurement analysis of free T4

Trimester	Estimated mean	Std. error	95% confidence interval	
			Upper Limit	Lower Limit
1st	16.4	0.2109	16.8417	16.0165
2nd	15.8	0.1964	16.2299	15.4539
3rd	15.1	0.1850	15.4544	14.7443

Multivariate repeated measurement analysis using Wilk's Lambda methods showed that this decline value of free T4 through the three trimester is statically significant with p value <.001 (Table 5).
Table 6: Showed Variation in the level of free TSH (µ IU/ml) trimester wise (N=145)

	1st Trimester	2nd Trimester	3rd Trimester
Mean	1.911	2.080	2.089
Standard Deviation	0.950	1.000	1.022
Min.	0.55	0.34	0.56
Max.	3.8	3.8	4.01

As table 6 the mean value of free TSH (µ IU/mL) of the 145 pregnant subject were found to be 1.911 +/- 0.95 (2 standard deviation) in the first trimester, subsequently the value slightly increase to 2.080 +/- 1.00 (2 standard deviations) in the second trimester and 2.089 +/- 1.02 (2 standard deviation).
Table 7: Multivariate repeated measurement analysis of free TSH

Trimester	Estimated mean	Std. error	95% confidence interval	
			Upper Limit	Lower Limit
1st	1.911	0.07895	2.0662	1.7662
2nd	2.080	0.08309	2.2438	1.9210
3rd	2.089	0.08487	2.2558	1.9227

Multivariate repeated measurement analysis using Wilk's Lambda methods showed that this decline value of free TSH through the three trimesters is statically significant with p value <.001
We estimated TPO antibodies in the first trimester of all 145 pregnant subjects. The normal reference value for TPO kit was <34 IU/mL as TPO negative and >34 IU/mL as TPO positive, Total 93.10% subjects were TPO negative and 6.89% subjects were positive for TPO antibodies.

DISCUSSION

The normal thyroid gland undergoes a profusion of physiological adaptions throughout the gestational period. These changes are reflected in the trimester wise variation of various functional parameters pertaining to the thyroid function. The present study is a follow-up study undertaken at the Antenatal clinic of a teaching hospital. The subject of the study included 145 apparently healthy young pregnant females attending the antenatal clinic in the first trimester. Serum-free T3, free T4 and thyroid-peroxidise antibodies (TPO Ab) were estimated by highly sensitive electrochemiluminescence immune assay (ECLIA). As per the manufacturer literature (Roche) the normal non-pregnant reference ranges were 2.8-7.1pmol/L for free T3, 12-22pmol/L for free T4, 0.3-4.2 UIU/mL for TSH and >34IU as TPO positive. We have also analysed their thyroid volume and echo texture in the three trimesters.
All the subjects in the study were comparable in their demographic data. The mean age of the women under study was 24.2 +/- 3.78 years (2 standard deviations). The average height and weight were 154.0 +/- 3.84 cm and 55.0 +/- 0.05 Kg respectively. The mean BMI was 22.3 Kg/m2.
The mean haemoglobin was 10.6 +/- 1.01 gm%. The mean serum calcium level of the 145 subjects in the first trimester was 8.72 +/- 0.71 mg/dl (normal 9- 10.5 mg/dl). The average values for serum phosphate and serum alkaline phosphates were 217.6 +/- 41.78 (normal 20- 120IU /L) respectively. Thus, our study demonstrated a two-fold increase in the value of alkaline phosphates during pregnancy in subjects belonging to the communities.

VARIATION OF FREE T3 AND FREE T4 DURING PREGNANCY

In our study, the serum free T3 levels were seen to decline progressively throughout study. The mean free T3 in the first trimester was 5.181 +/- 1.24 pmol/L (2 standard deviations), subsequently, it increased to 5.247 +/- 1.11 pmol /L in the second trimester followed by 5.246 +/- 1.08 pmol /L in the third trimester. This is shown in the table 7 and 8.Glinor and colleagues have studied 606 pregnant women in Belgium where iodine intake is marginal. They found that the serum-free T3 determination by nonequilibrium dialysis fell from 5.0 +0.1 pmol / liter in the first trimester to 3.8 + 0.1 pmol/liter in thethied trimester (normal range 3 – 11 pmol/liter). Our study also has similar observations. The minimum free T3 in our study was 0.4 pmol/ L whereas maximum was 6.6 pmol/ L in the trimester with the range of 6.2 pmol / L. In the second trimester corresponding values were 1.2 pmol /L and 6.97 pmol / L with a range of 5.77 pmol / L. Similarly, in the third trimester the minimum free T3 was 0.8 pmol / L while the maximum being 15.5 pmol / L, thereby the range of 14.7 pmol/L.In our study the serum free T4 levels also showed parallel changes, the level declined from first trimester to the thied trimester. The mean value of free T4 was 16.4 +/- 2.53 pmol / L (2 standard deviation) in the first trimester, subsequently the value decreased to 15.8 +/- 2.368 pmol / L in the second trimester followed by 15.1 +/- 2.22 pmol/L in third trimester. The fall in mean free T4 was 19.6% through the first to third trimester. This declining trend was statistically significant (p <.001) in our study by repeated measurement multivariate analysis. This is shown in the table 8 and 9. In the study by Glinoer and colleagues serum free T4 determination by non eqilibrium dialysis decreased from 17.9 + 0.3 pmol/ liter in the first trimester to 13.4 + 0.1 pmol/liter in the third trimester (nomal range lo- 26 pmol/liter) which is a similar trend as in our study. The minimum free T4 in our study was 2 pmol /L whereas maximum was 20.6 pmol /L in the first trimester with the range of 18.6 pmol / L . In the second trimester corresponding values were 7.6 pmol /L and 16.8

pmol / L with a range of 9.2pmol /L. Similarly, in the third trimester the minimum free T4 was 6.8 pmol /L while the maximum being 39.9 pmol/L, thereby the range of 33.1 pmol /L.

As described by Roti et al., earlier there was conflicting data regarding the variation of free hormone estimation due to the flaws in the methodologies employed for the determination of both free T4 and T3. However, most studies show decline in the free hormone level. In contrast the level of total T3 and T4 rise sharply between 6 and 12 weeks and progress slowly to stabilise around mid gestation by 20 weeks.In the study by kumar A et al mean T3 values were 1.35 > 0.30 pmol/L(2 standard deviation) in the first trimester. These were seen to rise through second trimester. These were seen to rise through second trimester to a mean level of 1.55 > 052 pmol /L. The levels then declined in the third trimester to 1.30> 0.68 pmol /L. Similarly, mean T4 levels were found to be 12.65> 4.84 pmol / L in the first trimester. It was seen to rise through second trimester to a mean level of 12.78> 3.12 pmol L .The levels than decreased in third semester to 12.60> 2.20 pmol / L. In pregnancy, the alterations in total thyroid hormone levels are the direct consequence of the marked increase in serum Thyroxine binding globulin (TBG). It is estimated that serum T4 concentrations increase by 1-3 %per day over the trimester to compensate for the above – mentioned increase in TBG.In our study both the levels of free T3 and T4 decreased during pregnancy. The reason for this is again the rise of TGB as due to increased concentration of bound hormone, little is left free in the circulation. However, the reason for the reduction in free hormone levels during the second half of gestation, observed in healthy women who have an adequate iodine supply, is not understood. Secondly, despite the fall in the levels of free hormone throughout the pregnancy, women in our study still were in thyroid state – a constant finding in the study by both Glinor and Colleagues in Belgium and kumar A et al in India

VARIATION OF SERUM TSH DURING PREGNANCY

In our study the mean serum TSH in the first trimester was 1.911 +/- 0.95 µ IU /ml (2 Standard deviation) whereas the non-pregnant values are 0.3 - 4.2 µIU /ml. The levels subsequently were found to increase to 2.080 +/- 1.00 µ IU /ml in the second trimester and eventually reaching 2.089+ /- 1.02 µ IU /ml in the third trimester. The variation of TSH level is shown in table 11. This increasing trend was also statistically significant in our stud. ($p < 0.001$) by repeated measurement multivariate analysis as shown in table 11. The maximum TSH in our study was 3.8 µ IU /ml in the first trimester with the range of 9.83 µ IU /ml followed by second trimester. Similarly in the third trimester the maximum TSH was 4.01 µ IU /ml.

Kumar A et al in their study from Delhi showed similar results. In their study the mean TSH levels were 1.00< 1.06 µ IU /ml (2 standard deviation) in the first trimester. The levels increased to 1.37<0.98 µ IU /ml in the second trimester and further in the third trimester of pregnancy to 1.74<1.02Uiu/Ml .Therefore, TSH levels were seen to rise progressively through the three trimesters of pregnancy. The apparent difference in the TSH levels in our study might be explained on the basis of difference in the immunonassay technique in these two studies. Secondly the population under study by Kumar A et al comprised of these groups of pregnant females belonging to the different trimesters whereas the present study was a fellow up study where sae subject was followed from first to third trimester.

The pattern of variation in the serum TSH during pregnancy in our study is typical of areas with moderate iodine deficiency as shown in the Belgium and Danish study where TSH follows an increasing trend from first to third trimester. The Dutch study in an iodine replete area failed to show a significant difference in serum TSH level between the third trimester and non pregnant control.

IODINE DEFICIENCY AND SERUM TSH LEVEL

Iodine deficiency is quite endemic in India. The prevalence of iodine deficiency disorder in the urban pregnant population of Delhi is estimated to be 22.9% by UmeshKapil et al. The physiological changes in thyroid function are significant in areas of iodine deficiency. During gestation there is a increased requirement of T3 and T4 to meet the increased metabolic demands of pregnancy. Secondly, increased glomerular filtration rate (GFR) leads to increased clearance of iodine during pregnancy. Thus, due to reduced availability of iodine coupled with the increased physiological demand the TSH levels are raised. Recently a study by J.H Lezarus in 2005 has shown that in iodine deficient and iodine sufficient areas, low maternal circulating thyroxin levels have been associated with a significant decrement in child IQ and envelopment. These data suggest the advisability of further evaluation for a screening program early in pregnancy to identify women with hypothyroxinaemia, and the initiation of prompt treatment for its correction.The relatively lower level of TSH in our study and similar findings by Kumar A et al could be because human chorionic gonadotropins (HCG) is having identical alpha-subunit to TSH and has weak thyrotropic activity. The HCG titre reaches peak towards the end of first trimester. Serum TSH titres show a decreases only during the first trimester of pregnancy because of negative correlation with HCG levels. Hence maternal serum TSH levels return to normal in second trimester and then rise in the third trimester.
In the third trimester the levels reach the higher limit of normal in our study, this is probably because the population in Delhi is not severely iodine deficient and also due to increased availability of iodised salt. However definite estimation of urinary iodine are required to substantiate the prevalence of iodine deficiency in our study group.

CONCLUSION

In this cohort study assessing thyroid function during pregnancy, we observed significant variations in serum free T3 (FT3), free T4 (FT4), and thyroid-stimulating hormone (TSH) levels across trimesters. FT3 levels remained within the physiological range, with minor fluctuations between trimesters. In contrast, FT4 exhibited a declining trend from the first to the second trimester. TSH levels, inversely related to FT3 and FT4, showed a gradual increase throughout pregnancy, although remaining within normal ranges.

The lower TSH levels in the first trimester can be attributed to the peak of human chorionic gonadotropin (hCG), which has TSH-like activity and exerts negative feedback on TSH secretion. These dynamics emphasize the importance of trimester-specific reference ranges for thyroid function tests in pregnant individuals.
Notably, 7% of subjects tested positive for thyroid peroxidase antibodies (TPO Ab), which elevated their risk of future overt or subclinical hypothyroidism. These findings underscore the need for vigilant monitoring of thyroid function during pregnancy and the consideration of individualized reference ranges.
In clinical practice, applying non-pregnant reference ranges to pregnant women can lead to misinterpretation of thyroid function. Therefore, healthcare providers should utilize trimester-specific reference intervals to accurately assess thyroid health in pregnant individuals, ensuring optimal care for both mothers and their developing fetuses.

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