

UTILITY OF THYROID FUNCTION TESTS IN PREGNANCYSoumya B.A¹, Nagaraja S², Dileep Vaman Deshpande³**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Pregnancy is associated with significant but reversible changes in thyroid function tests and the diagnosis of abnormality in the thyroid function during pregnancy is important for the wellbeing of both the mother as well as the fetus. The reference values of serum total tri-iodothyronine (TT₃), total thyroxine (TT₄) and Thyroid Stimulating Hormone (TSH) in non-pregnant women are not applicable during pregnancy and also differ in iodine deficient areas. **AIM:** The present study was carried out to study the variations in the thyroid function tests during normal pregnancy. **METHOD:** 30 apparently normal pregnant women in their first trimester between 20-35 yrs. of age were selected from obstetrics outpatient department of a tertiary Hospital in Davangere. 30 normal non-pregnant women were selected randomly from general population. Estimation of serum TT₃, TT₄ and TSH were done by Chemiluminescence immunoassay method. **RESULTS:** Data analyzed using unpaired student t-test. Serum TSH was significantly low in pregnant women with mean TSH→0.85μIU/ml than controls with mean TSH→1.65μIU/ml. Though serum TT₄ level was high in pregnant group, the difference was not statistically significant. **CONCLUSION:** Blunting of serum TSH could be due to thyrotropic action of elevated human Chorionic Gonadotropin (hCG) near the end of the 1st trimester. Thyroid Binding Globulin (TBG) induced by estrogen and relative iodine deficiency state in pregnancy leads to a rise in thyroid hormones which is vital for the normal fetal development. Hence thyroid function tests in pregnancy should be interpreted against gestational reference intervals to avoid misinterpretation of thyroid function in pregnancy.

KEYWORDS: Pregnancy, thyroxine, triiodothyronine, TSH, hCG, TBG, reference values.

INTRODUCTION: Pregnancy is a process by which the life of a baby begins in the mother's womb and progresses up to the stage when it is safe to expose the baby to the external world. It has been estimated that more than 200 million women from ages 14 to 44 years will be pregnant in any given year.¹

Due to the specific conditions related to the pregnancy period, there are various alterations including the biochemical parameters of thyroid function, accompanied with this phase of life. Pregnancy is associated with significant but reversible changes in the thyroid function studies, which are seen as a result of normal physiological state. Proper maternal thyroid function during pregnancy is important for the health of both the mother and the developing child.

The maternal thyroid hormones are critical to fetal neurodevelopment and embryogenesis; which change significantly during pregnancy. Iodine deficiency at critical stages of development in fetal life and early childhood remains the world's single most important and preventable cause of mental retardation.²

Pregnancy is accompanied by profound alterations in thyroidal economy resulting from a complex combination of factors specific for the pregnancy state such as rise in Thyroxine Binding Globulin (TBG) concentration, effects of human Chorionic Gonadotropin (hCG) on the maternal

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thyroid, alterations in the requirement for iodine, modifications in autoimmune regulation and the role of placenta in deiodination of iodothyronines.³

Hemodilution, in addition to the above said physiological changes could affect the functioning of thyroid gland and the interpretation of the thyroid function tests.⁴

The findings associated with the hypermetabolic state of normal pregnancy, can overlap the clinical signs and symptoms of thyroid disease. Both normal pregnancy and pregnancy complicated by conditions like hyperemesis gravidarum, can be associated with the thyroid function study changes that are strongly suggestive of hyperthyroidism in the absence of primary thyroid disease.⁵

Hence the study of thyroid function in normal pregnancy has a great value in the formulation of strategies for health care which necessitates a trimester specific reference range for thyroid hormones in pregnant women in a particular geographical area.

The values of serum tri-iodothyronine (T₃), thyroxine (T₄) and thyroid stimulating hormone (TSH) in non-pregnant women are not applicable during pregnancy and also differ in iodine deficient areas. It is important to understand the physiological changes that occur during normal pregnancy to differentiate it from hypo or hyperthyroidism.

This study is aimed at emphasizing the effects of normal pregnancy on thyroid hormone levels and thereby helping to distinguish it from that of pathological changes.

AIMS AND OBJECTIVES: This study was aimed to study the changes in maternal thyroid function - levels of serum total triiodothyronine (TT₃), total thyroxine (TT₄) and TSH in the first trimester of normal pregnant women between 20 – 35 years of age group and also to compare the same with normal non-pregnant women of the same age group.

METHODOLOGY: 30 normal healthy pregnant women in their first trimester of pregnancy between 20–35 years were selected consecutively as and when they presented to the Obstetric Department of a tertiary Hospital in Davangere. 30 normal non-pregnant women of the same age group were selected randomly from the general population.

Following an explanation about the nature and purpose of the study, those subjects who were willing to participate in the study were included after obtaining informed consent.

A detailed assessment was done and a pretested structured proforma was used to record the relevant information from each individual case selected. Data acquisition was performed in the morning.

The subjects who were selected underwent a detailed general physical and systemic examination. Physical examination of all the subjects included measuring height in centimeters, weight in kilograms, and recording of resting pulse rate by palpating the radial artery and blood pressure recording with a mercury sphygmomanometer using the appropriate sized cuff. Clinical examination of the cardiovascular, respiratory and abdominal systems was done in detail.

Following detailed assessment of the subjects, they were screened for the presence of inclusion and exclusion criteria and dropped if any exclusion criteria were present.

Inclusion Criteria:

- 1) Normal healthy pregnant women in 1st trimester of pregnancy in the age group of 20–35 years as the study group.
- 2) Normal healthy non-pregnant women between 20–35 years of age as the control group.

Exclusion Criteria:

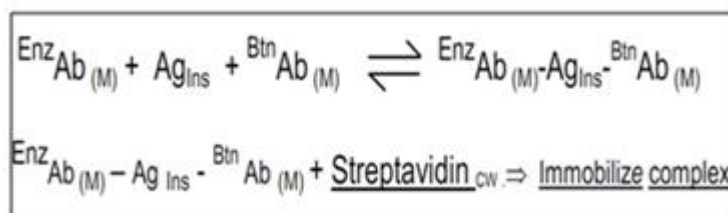
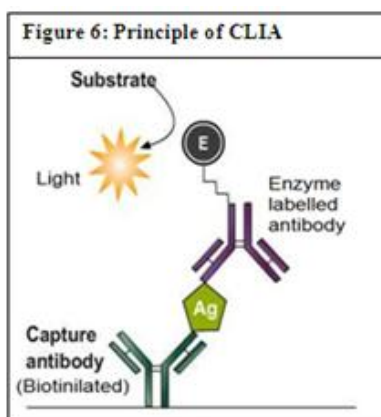
1. Age below 20 years and above 35 years.
2. History of thyroid dysfunction.
3. History of diabetes or hypertension.
4. High risk pregnancy.
5. Women with severe anemia.
6. History of liver/renal diseases.
7. History of multiple gestations.
8. History of previous adverse pregnancy outcome.

Investigations: 5ml of venous blood was drawn from the antecubital vein with aseptic precautions in a plain sterile bulb and serum were separated by centrifugation, then estimation of serum TT₃, TT₄ and TSH were done using thyroid profile Chemiluminescence Immunoassay (CLIA) kit from Acculite-Monobind in LUMAX 4101 CLIA microplate reader.

Estimation of serum TT₃, TT₄ and TSH:

Method: Chemiluminescence immunoassay method (CLIA)

Principle: In this method, the monoclonal biotinylated antibody (B^{tn} Ab_(m)), the enzyme labeled antibody (E^{nz} Ab_(p)) and the test serum containing the native antigen (Ag_{T₃/T₄/TSH}) are mixed which results in formation of a soluble sandwich complex (E^{nz} Ab_(p)-Ag_{T₃/T₄/TSH}-B^{tn} Ab_(m)). After equilibrium is attained, the bound fraction is separated and the enzyme activity is measured by production of light as Relative Light Units (RLUs). Value of RLU is proportional to amount of immobilized sandwich complex and hence to concentration of antigen (T₃/T₄/TSH) in serum.



Normal range:Serum TT₃: 0.5 – 2.0 ng/ml.Serum TT₄: 4.8 – 11.6 µg/dl.

Serum TSH: 0.28 – 5.45 µIU/ml.

Statistical analysis: Results were expressed as Mean ± Standard Deviation and analyzed using SPSS software. Unpaired student t-test was used for group comparisons. If 'p' Value >0.05 → Not Significant (NS); <0.05 → Significant(S); <0.001 → Highly Significant (HS).

RESULTS: A total of 30 normal pregnant women in first trimester in the age group 20 – 35 years were included as study group and 30 non-pregnant women as controls in the study (Table-1).

The mean age (in years) was 24.97 and 23.33, in controls and pregnant women respectively. There was no significant difference in the age between the two groups (p>0.05). (Table-1).

Mean height (in centimeters) was 153.5 in controls and 154 in the first trimester pregnant women. There was no significant difference (p>0.05) in the height between the non-pregnant and pregnant women.

The median weight (in kilograms) was 50.5 and 51 in the controls and pregnant women in the first trimesters respectively. There was no significant difference in weight among the two groups (p>0.05). (Graph-1).

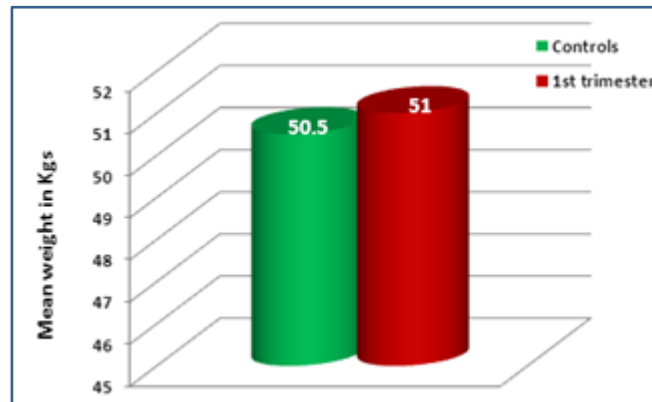
Changes in thyroid profile (Graph - 2): Serum TSH was significantly low in pregnant women with mean TSH→0.85µIU/ml than controls with mean TSH→1.65µIU/ml. Though serum TT₄ level was high in pregnant group, the difference was not statistically significant

TABLES AND GRAPHS:

Age group (years)	Controls	1 st trimester
20 – 22	5	9
23 – 25	13	13
26 – 28	10	5
29 – 30	2	3
Total	30	30
Mean Age (years) ± SD	24.97	23.33

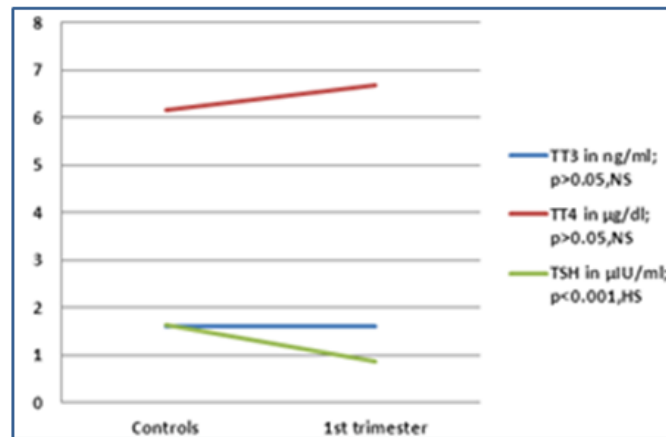
TABLE 1: AGE WISE DISRTIBUTION**p > 0.05, NS**

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GRAPH 1: COMPARISON OF WEIGHT IN TWO GROUPS

$p > 0.05$, NS



GRAPH 2: COMPARISON OF TT₃, TT₄ AND TSH BETWEEN THE TWO GROUPS

DISCUSSION: Pregnancy is associated with remarkable changes in the functioning of the thyroid gland and plays an important role in pregnancy outcome as well as in fetal development. The changes caused by pregnancy in the mother establish a new homeostatic equilibrium starting from the time when the zygote is implanted and ending only at the time of puerperium. Thyroid disorders are associated with higher rate of preeclampsia, spontaneous abortion, premature delivery, intra uterine fetal death and disturbed fetal psychomotor development.⁶

Therefore, understanding the nature and the magnitude of the changes that occur in pregnancy is important to differentiate pregnant women with thyroid diseases from those with adaptive changes due to pregnancy.

Changes in serum TSH levels: In this study, it was seen that there was a significant decrease in serum TSH level in pregnant women in first trimester when compared to controls. The blunting of serum TSH levels could be due to the thyrotropic action on the thyroid gland of elevated serum

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concentrations of hCG near the end of first trimester, with a mirror image between peak hCG values and a nadir of serum TSH values.

TSH and hCG contain a common α subunit and share 85% sequence homology in the first 114 amino acids and 12 cysteine residues at highly conserved positions, their tertiary structures are very similar. Hence, increased hCG levels in the first trimester can cause excessive stimulation of the thyroid gland. Both the amplitude and duration of peak hCG values gear the changes in thyroid function.

It has been shown that purified hCG increases iodide uptake, increases cyclic-AMP production dose dependently and stimulates organification and T_3 secretion.⁷ A 10, 000 IU/L increment in circulating hCG corresponds to a lowering of serum TSH of 0.1mIU/L.³

Hypersensitive TSH receptors due to missense mutation have been observed in pregnant women with gestational hyperthyroidism and hyperemesis gravidarum. Gestational hyperthyroidism could also be caused by a variant of hCG with increased thyroid stimulating activity which is supported by the finding that hCG fraction containing asialo-carbohydrate chains was significantly increased in hyperemetic pregnant women with thyrotoxicosis compared to controls.⁸

Similar findings were also reported in earlier studies by Pasupathi et al,⁵ Kumar et al,⁹ Antonini et al,⁶ Jabbar et al,¹⁰ Thevarajah et al,¹¹ Zhargami et al¹² and Santiago et al.¹³

In a study by Das et al,¹⁴ there was no suppression in the TSH levels during pregnancy, suggesting that the women during this stage were not probably hyperthyroid. They proposed that with the advancing pregnancy the binding of T_4 with TBG is significantly disturbed by the presence of some unknown metabolites arising from pregnancy, which can displace and bind T_4 molecules from TBG. The displaced bound T_4 moiety thus becomes physiologically ineffective. This would cause a less proportionate rise in thyroxine binding capacity in comparison to the marked rise in serum TBG level.

Changes in serum TT_3 and TT_4 levels: This study shows that though there was a rise in serum levels of TT_4 , it was not statistically significant. These changes in thyroid hormones could be attributed to the increase in Thyroxine Binding Globulin (TBG), which is induced by estrogens and starts rising early in pregnancy, continues in linear fashion till 20 weeks of gestation and persists until delivery. As a consequence, serum levels of TT_3 and TT_4 rise in the first and second trimesters till the third trimester of pregnancy and then decline till term. This may be important for normal fetal development.⁹

During pregnancy, the half-life of TBG extends from 15 minutes to 3 days and its concentration triples by 20 weeks gestation,¹⁵ due to estrogen driven glycosylation contributing to the increase in thyroid hormone levels.

Increased sialylation mediated by estrogens, reduces the hepatic clearance of TBG, resulting in increased levels of both TT_3 and TT_4 .

Since the hCG and TSH share identical α subunits and have similar β subunits and receptors, in the first trimester a hormone spillover syndrome can occur in which hCG stimulates the TSH receptor and gives a biochemical picture of hyperthyroidism. This is particularly common in multiple pregnancy, trophoblastic disease and during hyperemesis gravidarum, when concentration of both hCG and thyrotropic subtypes may be greater.¹⁵

Type III deiodinase (D_3), produced by the placenta, converts T_4 to rT_3 and T_3 to diiodotyrosine and has extremely high activity during fetal life. Increased demand for T_4 and T_3 has

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been suggested to increase the production of these hormones which ultimately increases the circulating concentrations of the hormones.

Changes in albumin and free fatty acid concentrations sustain the binding of T_4 and T_3 to carrier proteins; which decrease the free hormonal levels and further stimulate T_4 and T_3 production. In a study by Kabyemela et al,¹⁶ the mean values of T_3 and T_4 during pregnancy were about 1.5–2 times higher than in healthy non-pregnant women. Whitworth et al¹⁷ found levels of T_4 above the reference range in 90% of the pregnant subjects studied. Glinoyer et al¹⁸ found 50% of their subjects in the third trimester with T_4 levels above the non-pregnant reference range.

Findings similar to our study was reported by Pasupathi et al,⁵ Erem et al,¹⁹ Jabbar et al¹⁰ Kumar et al⁹ and Zhargami et al.¹²

As the rapid rise in serum hormone binding capacity due to increased serum TBG levels tends to induce a trend toward slightly decreased free hormone concentration, thyroidal adjustment has to be regulated. This is done primarily through the normal pituitary thyroid feedback mechanism that is by TSH stimulation of the thyroid gland. In healthy pregnant women, the extra load on the thyroid machinery is relatively minor and the accompanying physiological changes are unnoticeable.

Not every pregnant woman, who demonstrates elevated T_4 , is really in a state of hyperthyroidism; but it is the new physiological condition which necessitates extra thyroxine requirement. T_4 is elevated, not for the sake of hyperthyroidism, but for the demand of the growing fetus and the maternal physiological conditions. Therefore the establishment of the reference intervals and the methodology of the thyroid hormone measurements in each region is a great importance.

CONCLUSION: Blunting of serum TSH could be due to thyrotropic action of elevated human Chorionic Gonadotropin (hCG) near the end of 1st trimester. Thyroid Binding Globulin (TBG) induced by estrogen and relative iodine deficiency state in pregnancy leads to rise in serum TT_3 and TT_4 which is vital for the normal fetal development. Hence thyroid function tests in pregnancy should be interpreted against gestational reference intervals. Clinical use of the results of this study may be useful in establishing reference values for our population; thus minimizing the possibility of misinterpretation of the thyroid function test results of pregnant women in our research area. These results demonstrate the need to recommend and promote thyroid function tests as a mandatory investigation for every pregnant woman along with the other routine ones to aid in the detection of preventable cause of mental retardation.

Limitations: Though our study is by no means exhaustive, it does provide a glimpse into the variety of adaptations in thyroidal economy during normal pregnancy; which brings about changes in the levels of TT_3 , TT_4 and TSH in the absence of any thyroid disorder. Although we understand to some extent these changes and also since only very few studies have been done on this aspect, further research is needed to study the effect of normal pregnancy on thyroid function.

It has been suggested that changes in free hormonal levels are more sensitive than the total hormonal levels in assessing the thyroidal dysfunction. This study gives quantitatively and qualitatively more effective results, if the estimation of free hormonal levels and serum iodine are included along with TSH and the total hormonal estimation.

This study may give more accurate results if the same subjects were taken as controls before pregnancy and were followed during pregnancy, which could not be done in this study because of time factor. Hence further studies are needed to evaluate the effect of normal pregnancy on thyroid function.

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