Original Article

Raised TSH Level Among Third Trimester

Insignificant Variation of Raised Thyroid Stimulating Hormone Level Among Third Trimester of Pregnancy in Diagnosing Subclinical Hypothyroidism

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ABSTRACT

Objective: To determine and compare the mean values of thyroid stimulating hormone in three trimesters of pregnancy, coming for antenatal workup in Al-Nafees medical college & Hospital Islamabad, Pakistan.

Study Design: Descriptive / Analytical study

Place and Duration of Study: This study was conducted at the Gynecology/Obstetrics and Pathology departments of Al-Nafees Medical College & hospital Islamabad from 1st Feb, 2018 to 31st Jan, 2019.

Materials and Methods: In this study random screening of 150 pregnant females for serum TSH levels was done to identify cases of SCH. Females were divided in to three equal groups i.e. 50 females in first, second and third trimester each. We measured serum TSH levels by using ELISA and take American thyroid association guidelines (ATA) for TSH levels in three trimesters as reference values. Trimester specific cut off values of TSH as given by ATA guidelines were used for diagnosis of cases of SCH. Data were analyzed by SPSS version 20. The study design was cross-sectional.

Results: In our study we found a statistically insignificant variation of serum raised TSH amongst three trimesters as depicted by p-value >0.05.

Conclusion: It may be inferred from above mentioned results that there was no significant variation seen in TSH levels of patients with subclinical hypothyroidism in our local setting (females coming to ANMC&H for antenatal care) amongst three trimesters. Results of this study suggest that a single TSH value irrespective of trimester specific cut offs can be used to label a female as having SCH. Timely diagnosis will help clinicians to avoid maternal and fetal poor outcomes associated with SCH as documented in various studies on thyroid disorders.

Key Words: Subclinical hypothyroidism, serum TSH levels, Obstetrical outcomes, ATA guidelines, Trimester specific cut off values for TSH

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INTRODUCTION

Subclinical hypothyroidism (SCH) is principally a biochemical disorder intensified more during pregnancy.

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Diagnosis of SCH is established when thyroid stimulating hormone (TSH) levels are elevated with a normal free thyroxin (FT4) levels.[1] There is an increased production of thyroxin (T4) and triiodothyronine (T3) by up to 50%, owing to several physiological and hormonal changes during pregnancy.[2] Physiological changes during pregnancy results in both increase in size of the thyroid gland as well as in iodine requirement. Fetal thyroid gland is not functional after 18-20 weeks of gestation and fetus is entirely dependent on maternal thyroid hormones after that period.[3] Pregnancy also intensifies the demands on the hypothalamic-pituitary-thyroid axis. As a consequence thyroid dysfunction is a common occurrence during gestation. Therefore, timely screening and management of both overt and subclinical hypothyroidism is very crucial. This will dramatically reduce the risk of adverse obstetric outcomes including fetal loss.[4] Although, the effects of overt hypothyroidism on pregnancy are well documented. Certain studies reported the adverse outcomes with SCH as well. These adverse obstetrical outcomes are include gestational

hypertension and miscarriages, associated more so with overt hypothyroidism.[5] Due to role of thyroid hormone on cardiovascular physiology and blood pressure regulation, likelihood of gestational hypertension is more when compared with euthyroid women.[6]Multiple other adverse obstetrical and fetal outcomes reported with SCH includes preterm labor, placental abruption, fetal distress, pre-eclampsia, gestational diabetes and preterm birth. This fact highlights the role of healthcare professionals working in antenatal care for early identification of thyroid disorders. ATA guidelines recommends trimester-specific reference ranges of TSH levels for making a diagnosis i.e. TSH range, first trimester >0.1mIU/L and <2.5mIU/L, second trimester <0.2mIU/L and >3.0mIU/L and third trimester >0.3 and <3.0 mIU/L.[7]As per the revised guidelines described by ATA and AACE, the serum TSH value of 4.12 mIU/l, is used to label a patient as SCH.[8] It was also accentuated that in order to label a case of SCH, reevaluation of TSH should be done within 2 weeks to 3 months. The expert panel also emphasized repeat testing of TSH levels every 6–12 months (4.5 and 10 mIU/l), before starting management.[9]

The present study was therefore planned to ascertain the relationship of serum TSH levels with advancing gestational age/trimester. It will also help us in making a diagnosis of SCH irrespective of gestational age/trimester. We can also determine that, SCH can be diagnosed anytime during gestational period, if a pregnant female came late for her 1st antenatal booking.

MATERIALS AND METHODS

After the approval of Ethical Review Board Committee (ERBC) ISRA University Islamabad, study was conducted in ANMC & H Islamabad, Pakistan in collaboration with Pathology and Gynecology/Obstetrics departments of same hospital. Sample Size was calculated to be 150 pregnant females by taking 11% prevalence of subclinical hypothyroidism in pregnancy.[10] The laboratory tests were conducted at the Multi-disciplinary laboratory (MDR) at ANMC & H Islamabad. This was a comparative cross sectional study done between 1st Feb, 2018 to 31st Jan, 2019. Sampling technique uses was non probability Convenience sampling

One hundred fifty pregnant ladies in any trimester of pregnancy visiting Obstetric department of ANMC & H for antenatal care with no signs or symptoms of thyroid disease or thyroid surgery were included in the study. Whereas, diagnosed cases of hypertension and ischemic heart disease and symptomatic hypothyroidism were excluded from the study. Pregnant females with history of preterm births, fetal anomalies or still births in previous pregnancies were also excluded from the study. History and examination findings were noted down on bio data proforma of each patient after taking consent on consent form. The serum separation was done from the sample in gel tube on same day, at 3000rpm for 05 minutes and preserved at -40C in aliquots for the estimation of TSH. The processing of TSH was done twice weekly by 3rd generation ELISA on micro plate-based ELISA. The sample processing was done as per recommended guidelines. The positive and negative quality controls were run with each batch for quality assurance. The results of serum TSH were documented on lab evaluation proforma. Trimester wise cut off values of TSH for labeling a case of SCH as given by ATA guidelines were taken as reference. After sample processing for TSH, leftover samples were saved in refrigerator of biochemistry lab for use in future.

Statistical Data Analysis: Data were analyzed using the Statistical Package for Social Sciences version 20 (SPPS 20). The numerical variables of TSH were used to assess statistical inference. Following statistical tests were used for qualitative and quantitative data analysis; Amongst the quantitative variables, mean values and the standard deviation were used in order to assess the accuracy of results amongst three trimesters of pregnancy. p-Value < 0.05 was considered as statistically significant. The frequencies were calculated in terms of percentages for SCH in three trimesters of pregnancy.

RESULTS

Samples for TSH were taken and processed as explained in methodology. Trimesters specific cut off values of TSH as described by ATA were taken as reference. Pregnant females having values of TSH greater than the cut off values given by ATA were labeled as having SCH.

Frequency Distribution of SCH: Regarding the frequency distribution of subclinical hypothyroidism out of the total 150 (N) participants, 34.91% (N=52) participants had found positive for SCH.

Table No. 1: Mean, SD and Occurrence Percentage of TSH

Group(n=50)	TSH Normal Range (mIU/L)	Frequency (SCH)	Occurrence (%)	Mean (SCH)	Standard deviation
Trimester-I	(0.1-2.5)	18	36.75	3.5	±0.57
Trimester-II	(0.2-3)	19	38	3.85	±0.66
Trimester-III	(0.3-3)	15	30	4.05	±0.73
Cumulative Occurrence Percentage	34.91 %(N=52)				

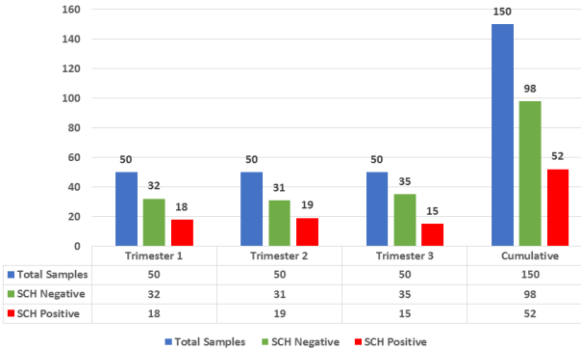

Figure No. 1: Frequency distribution of SCH positive and negative cases

Percentages of SCH cases in individual groups were 36.7% (n= 18), 38% (n = 19) and 30(n=15) in trimester I, II and III respectively as shown in Figure-I. Highest percentage of females positive for SCH was observed in second trimester as shown in Table-1.

Figure No. 1 is a representation of total number of samples along with both SCH positive and SCH negative cases in each group. According to the results 52 females were found to have raised TSH levels whereas 98 females showed normal TSH levels out of 150 females in our study population. When further analyzed for individual trimesters, 18 positive cases of SCH while 32 negative cases were found in first trimester. In second trimester, there were 19 positive cases of SCH while 31 negative cases found. In third trimester 15 positive cases of SCH were found out of total 50 subjects.

Analysis of Variance Applied to Tsh Levels: Table-2 shows results of ANOVA applied to mean and SD of TSH levels of each group. Analysis of variance (ANOVA) applied between TSH levels of SCH positive and SCH negative cases. The comparison in groups proved to be insignificant as depicted by p-value>0.05. It therefore wasn't followed by application of Post HocTukey test. It may be inferred from above mentioned results that there was no significant variation seen in TSH levels of patients with subclinical hypothyroidism in our local setting (females coming to ANMC&H for antenatal care) among three trimesters.

Results of this study suggest that a single TSH value irrespective of trimester specific cut offs can be used to label a female as having SCH.

Table No. 2: Comparison, using ANOVA, of TSH in Three Trimesters

Variable	Groups	Mean and SD	f-Value	p-Value
TSH	1st Trimester	3.51± 0.57	1.572	*>.05
	2nd Trimester	3.85± 0.66		
	3rd Trimester	4.05± 0.73		

*p-Value of ≤ 0.05 was considered significant

DISCUSSION

A meta-analysis was done to show the association of subclinical hypothyroidism in pregnancy with an increased probability of developing hypertensive disorders during pregnancy. During this study, it was evident that this association exists irrespective of the trimester. This study is consistent with our results that effects and occurrence of subclinical hypothyroidism are seen irrespective of gestational age. The only difference from our study is that they also analyzed SCH association with Hypertensive disorders.[12]

Another study was done to determine the association of various adverse outcomes of SCH as documented in other studies. They specifically analyzed these effects during the 1st trimester. As the exceedingly high circulating human chorionic gonadotropin levels and increased synthesis of thyroxin-binding globulin in the first trimester will lead to maternal thyroid hormone adjustment and result in a variety of thyroid disorders. But, their study also concluded that no remarkable adverse outcome seen in these patients and there no relationship found of changing TSH levels with trimesters.[13]

Results of a study done in Pakistan determine the prevalence of subclinical hypothyroidism (SCH) during their first trimester of pregnancy to be 37% in pregnant women. They also compared outcomes of SCH i.e. having higher risks of pregnancy loss, placental abruption, death of neonate when compared with euthyroid pregnant ladies. Whereas, they did not found any association of SCH with gestational hypertension, preterm labor, premature delivery or miscarriage, placenta previa and intrauterine growth restriction (IUGR).It was concluded that the effects associated with SCH are not linked to gestational age/trimester. Although, first trimester due to highest values of beta HCG have the highest probability of various adverse outcomes.[14]

This study clearly explained that there is an inverse relationship between HCG and TSH throughout pregnancy. Peak concentration of HCG in first trimester corresponds with the reduction of TSH secretion. After the first trimester (second and third trimesters) TSH slightly rises but it does not reach the pre-pregnancy levels. This concluded that throughout pregnancy irrespective of the trimester the range of normal serum total T4 (TT4) and T3 (TT3) concentrations remained higher because of a rapid increase in thyroxin-binding globulin (TBG) levels. So, a single TSH value can be used to label a case of SCH during pregnancy irrespective of the trimester.[15]

Results of a study done in Agha Khan University regarding the trimeter wise relationship of SCH during pregnancy were found to be comparable with studies done in other parts of world.

Hypothyroidism treatment in pregnancy is also an added concern on the health care setup, especially in a developing country like Pakistan. Another multi centre study reported higher TSH levels in 4.44% of women

diagnosed with overt as well as subclinical hypothyroidism. Considering the impact of hypothyroidism on pregnancy and fetus plus high prevalence, most evidence-based guidelines recommend adequate replacement of thyroid hormone not only during pregnancy but even before conception to reduce adverse outcomes.[16] This study also proved that no specific trimester is selected to label a female as SCH positive and to start management as evident from our study too.

Several other studies have analyzed the association of SCH with adverse outcomes during pregnancy and long-term outcomes in mothers and children. Results of these studies showed increased risks of these outcomes among women with untreated SCH. However, these studies still have heterogeneity regarding start and timing of initiation of levothyroxine. It was evident from this study too that no specific gestational period/trimester is labeled for diagnosing and starting treatment.[17]

CONCLUSION

It is concluded from our study that a single TSH level irrespective of the gestational age/trimester can be used to label a case of SCH.As, we compared the mean values of TSH amongst three trimesters, no significant variation was observed as evident by a p-value more then 0.05.

Author's Contribution:

Concept & Design of Study:	Beenish Zafar
Drafting:	Ayesha Mansoor, Roomisa Anis
Data Analysis:	Khizera Anwar, Sadia Aslam
Revisiting Critically:	Beenish Zafar, Ayesha Mansoor
Final Approval of version:	Beenish Zafar

Conflict of Interest: The study has no conflict of interest to declare by any author.

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