ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH INCREASED RISK OF RECURRENT MISCARRIAGES DURING ANTENATAL THYROID STIMULATING HORMONE SCREENING

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ABSTRACT

Objective: The present study was designed to ascertain the association of raised TSH in sub-clinical hypothyroidism with history of miscarriages in pregnant females coming to Al-Nafees Medical College Islamabad, for antenatal care.

Material and Methods: This Comparative cross-sectional study was conducted at department of Biochemistry, in assistance with Gynecology/ Obstetrics and Pathology department of Al-Nafees Medical College & Hospital Islamabad, Pakistan. 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 then observe association of the raised TSH levels with H_x miscarriages. Data were analyzed by SPSS version 20. Statistical methods used to analyze the data included mean ± SD, percentages, ratio, ANOVA and Pearson correlation tests

Results: The data obtained from this study indicates that 34.7% of females were found positive for SCH in our local population. Trimester wise reference values of TSH as given by ATA guidelines were used for diagnosing cases of SCH. In our study we found a statistically significant association of raised TSH levels with H_x miscarriages as depicted by a significant p-Value ≤ 0.001.

Conclusion: Therefore, it is concluded from our study that there is an increased incidence of miscarriages in SCH positive females in contrast to females with normal TSH levels. Therefore, this finding highlights the role of antenatal TSH screening to avoid maternal and fetal poor outcome i.e., miscarriages associated with raised TSH levels.

Key Words: Subclinical hypothyroidism, Serum TSH levels, Obstetrical outcomes, Miscarriages, Trimester specific cut off values for TSH.

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INTRODUCTION

Pregnancy effects multiple physiological functions of thyroid gland. Human chorionic gonadotropin (hCG) is the most significant factor in increasing the level of thyroid hormone during pregnancy. These normal physiological changes during gestation might render pre-existing mild thyroid dysfunction as gestational thyroid disease [1]. Subclinical hypothyroidism (SCH) is primarily a biochemical diagnosis with raised Thyroid stimulating hormone (TSH) levels and simultaneous normal thyroid hormone levels in an asymptomatic patient [2]. The Endocrine Society and European Thyroid Association (ETA) guidelines recommend levothyroxine replacement independent of the thyroid antibodies positivity status. American thyroid association (ATA) recommends Levothyroxine therapy in pregnant females (positive for TPO-Abs) with TSH greater than the pregnancy-specific reference range [3]. Various adverse effects of SCH include high risk of miscarriages, premature birth and lower offspring intelligence quotient. Trimester specific diagnostic criteria of SCH in pregnancy are given by ATA. According to ATA, TSH normal reference range is 0.1 to 2.5 mIU/L, 0.2 to 3.0 mIU/L and 0.3 to 3.0 mIU/L for the for first, second and third trimesters respectively [4].

Although there is a proven increased risk of miscarriages in overt hypothyroidism females as compared to ones with SCH. A recent large retrospective cohort study involving 5405 pregnant women with SCH, thyroxine replacement was associated with reduced miscarriage. Current recommendations therefore support thyroxine for TSH >4 mIU/L along with the thyroid antibodies' positivity status [5].

To avoid recurrent pregnancy loss (RPL) resulting from this high proportion of undiagnosed

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females with SCH, serum TSH <2.5 mIU/L is recommended. This reference value is recommended for both, the women planning to conceive as well as for pregnant women [6]. Thyroid hormone derangements are amongst the most common endocrine disorders resulting in spontaneous abortion and miscarriages. Abalovich *et al*. showed that untreated hypothyroidism either subclinical or overt is linked with increased frequency of miscarriages in contrast to females with normal TSH levels [7]. Antenatal screening of SCH during pregnancy help us to detect apparently asymptomatic individuals who are at an increased risk of a full-blown thyroid disorder. The screening test for SCH should be simple, safe and cost effective with reliable reference ranges [8].

In view of the high prevalence of SCH during pregnancy and its association with poor fetal outcomes, this study is planned to get statistics regarding the association of SCH with Hx of miscarriages in pregnant females. There is a need of regular antenatal screening of pregnant females for subclinical hypothyroidism especially those having positive past Hx recurrent miscarriages. This will help us to get an insight regarding this significant association between SCH and Hx of miscarriages and to suggest that TSH screening should be included in routine antenatal workup. This practice will overall improve the maternal and child health care in our population and also to reduce the incidence of recurrent miscarriages.

MATERIAL AND METHODS

This comparative cross-sectional study was carried out at Al Nafees Medical College and hospital Islamabad, Pakistan in assistance with Pathology and Gynecology/Obstetrics department Islamabad from February, 2018 to January, 2019. Sample size was calculated to be 150 pregnant females by taking 11% prevalence of SCH.

Pregnant females in any of three trimester of pregnancy visiting Obstetric department of ANMC & H for antenatal care, who were completely asymptomatic for thyroid disease were included in this study. Whereas females with hypertension, ischemic heart disease, symptomatic hypothyroidism and with history of preterm births, fetal anomalies or still births in previous pregnancies were omitted from this study.

Institutional Ethical review board committee of Al Nafees Medical College and Hospital, Islamabad approved this study proposal. A written and informed consent was taken before taking blood samples from the enrolled participants.

A detailed biodata proforma was filled before taking blood samples. Detailed obstetrical history from the enrolled participant was taken regarding previous history of miscarriages/abortions, still birth or Hx of fetal anomalies. Sample collection was done by using convenient sampling technique of enrolled 150 pregnant females, which were divided into three equal groups according to trimesters with 50 females in each group e.g., 50 females in each trimester.
Females were labeled as SCH positive by using ATA trimester specific cut-off values by estimating serum TSH levels.

Sampling was done from OPD of Gynecology/ Obstetrics department of Al Nafees medical college & hospital. Blood samples were collected in serum gel bottles for TSH estimation. The serum separation was done from the sample in gel tube on same day, at 3000rpm for 05 minutes and preserved at -40^{o}C in aliquots for the estimation of TSH. The processing of TSH was done twice weekly by 3rd generation ELISA on micro plate-based ELISA [9]. Left over samples were saved and stored at –4^{0}C in Pathology lab of ANMC&H for future use.

Statistical Analysis: Statistical methods used to analyze this study included mean ± SD, percentages, ratio, ANOVA and Pearson Correlation tests.

RESULTS

Results were analyzed by using SPSS version 20. A total of 150 pregnant females e.g. 50 females in each first, second and third trimester respectively were analyzed in this study. Regarding the frequency distribution of subclinical hypothyroidism out of the total 150 (N) participants, 34.91% (N=52) participants had found positive for SCH. 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 Figure-I.

Correlation of TSH level with history of miscarriages: Table-I is showing the mean TSH levels in females with and without Hx miscarriages. As shown in this table mean TSH levels in females with positive Hx miscarriages were on the higher side as compared to the females with negative Hx. Table-II(a) is showing the total number of miscarriages both in SCH positive as well as SCH negative females. As illustrated in this table the numbers of miscarriages were higher in SCH positive females. This significant association between the two (raised TSH and positive Hx miscarriages) is also depicted in the table-II(b) by a significant p-Value of ≤0.01.

Table-I: Mean TSH levels in cases with and without miscarriages.

Mean TSH Level (mIU/L)					
Miscarriage			No Miscarriage		
Trimester 1	Trimester 2	Trimester 3	Trimester 1	Trimester 2	Trimester 3
2.7	3.2	3.25	1.17	1.65	1.29

Table-II (a): Total number of miscarriages in SCH(-ve) & SCH(+ve) females.

	Trimester 1 (Miscarriages)		Trimester 2 (Miscarriages)		Trimester 3 (Miscarriages)	
	YES	NO	YES	NO	YES	NO
SCH (-ve)	6	26	8	23	5	30
SCH (+ve)	12	6	15	4	9	6

Table-II(b): Association of TSH levels with miscarriages.

TSH	Variable	p Value
	H_x Miscarriages	**0.00

* Significant p ≤ 0.05, **Highly significant p≤0.01

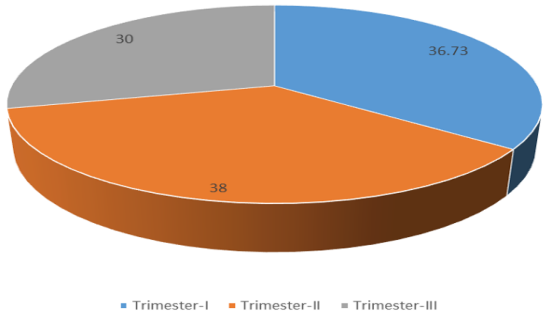
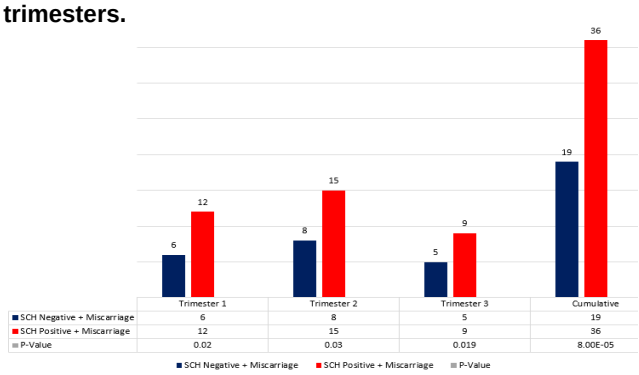
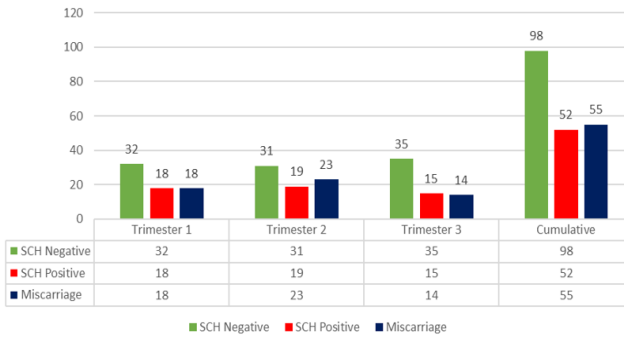


Figure-I: Percentage Distribution of SCH in three trimesters.



* Significant p ≤ 0.05, **Highly significant p≤0.01

Figure-II: Comparison of miscarriages cases with positive & negative SCH



*Significant p ≤ 0.05, **Highly significant p≤0.01

Figure-III: Frequency of miscarriages, SCH positive & SCH negative.

As shown in this Figure-II and Figure-III cumulatively 36 cases were positive for SCH and also had positive history of miscarriages whereas 19 cases were negative for SCH and had a positive history of miscarriages. These results clearly showed that there was marked difference between the positive H_x of miscarriages in SCH cases as compared to SCH negative cases. This association of H_x miscarriages was also analyzed amongst three trimesters. Results of individual trimester showed that in first trimester 12 SCH positive cases had Hx of miscarriages. In second trimester 15 SCH cases had Hx of miscarriages and in third trimester 9 SCH had positive Hx miscarriages out of total 50 pregnant females in each trimester. Figure-III showed overall cases with positive Hx miscarriages (n=55) out of which 52 cases were positive for SCH. This bar chart showed a clear association of raised TSH with Hx miscarriages. Bar chart (Figure-II & III) showed highly significant association between Hx miscarriages and raised values of TSH (SCH) in all three trimesters as depicted by a p-Value of < 0.05.

DISCUSSION

Subclinical hypothyroidism primarily considered as a biochemical disorder with elevated TSH levels. The untreated disease results in poor obstetrical outcomes i.e. miscarriages, gestational hypertension, preeclampsia, pre-term delivery, low birth weight, placental abruption and postpartum hemorrhage [10]. It is postulated in certain studies that risk of pregnancy loss/miscarriages is much greater in women with untreated SCH compared with euthyroid pregnant women. This finding is depicted with a significant p-Value of <0.01 in these studies. However, the rate of miscarriage did not significantly vary among women with treated SCH compared with

euthyroid women [11]. In our study we also found a significant association of miscarriages with SCH as depicted with a p-Value of < 0.05. The only difference between our study and above said study is that, we did not study the autoimmunity status of the females with SCH.

A meta-analysis conducted by Sheehan *et al*. and Chan *et al*., results of which also showed an insignificant association of miscarriages, stillbirths and perinatal losses with subclinical hypothyroidism [12]. This meta-analysis is again in contrast to our study, as we found a significantly higher frequency of miscarriages in women positive for SCH. A study conducted in Japan to determine the effects of raised TSH or SCH with adverse maternal outcomes. They compared the results of two groups, one with raised TSH and one with normal TSH. Results of this study showed no significant association of raised TSH with spontaneous abortion and miscarriages [13]. This study is also in contrast to our study in which we randomly screen pregnant females in three trimesters of pregnancy and found significant association between raised TSH and miscarriages.

Another study was conducted to see the effect of borderline raised TSH levels on poor obstetrical consequences i.e. recurrent pregnancy loss. This study also revealed that although the frequency of pregnancy loss is high in borderline SCH but statistically results were insignificant. Another study depending on literature database conducted from January 1, 1980, to December 31, 2015 to evaluate the association between SCH and the risk of miscarriage before 20 weeks of pregnancy. In this, basically those studies were selected which compared the prevalence of miscarriages in pregnant females with raised TSH and pregnant females with normal TSH values. After statistical analysis they found that patients with untreated SCH had a high prevalence of miscarriages as compared to pregnant women with normal thyroid hormone levels. These results were also found statistically significant which were showed by a p-Value of 0.02 [14]. This study is in accordance with our study in which we also found a significant association of miscarriages with SCH with a p-Value <0.05.

In another study done on pregnant women from Peking Union Medical College Hospital and Haidian Maternal and Child Health Hospital from July 2011 to December 2012, they evaluated the utilization of timely SCH screening and intervention and its effects on pregnancy outcomes. In this study they screened for SCH (on the basis of Thyrotropin levels 2.5-10 mIU/L). They found that incidence of miscarriages was reduced considerably in SCH positive cases who receive replacement with thyroxine. Their study concluded that timely screening and intervention can reduce the risk of miscarriages [15].

In contrast to this study, we took trimester wise reference intervals as given by ATA guidelines instead of taking a broad range of TSH levels 2.5-10 mIU/L for labelling a case as of SCH. This study is in accordance with our study that we also found significant association between history of miscarriages and SCH as depicted by a p-Value of <0.05. Another study conducted to find out the effect of thyroid disorders including SCH, euthyroidism and overt hypothyroidism on live birth rates and miscarriages. Results of this study showed that the live birth rate was 45% and 52% whereas rate of miscarriage was 35% versus 28% in women with subclinical hypothyroidism compared to euthyroid women respectively [16,17]. This study is in contrast to our study as we found a significant association of miscarriages with SCH.

A prospective cohort study was done in four medical centers of the United States done on healthy women, of age group between 18-40 y, who were actively attempting to conceive and had one or two previous pregnancy losses were included in the study. Their TSH levels were measured and they found that cases with TSH levels >2.5mIU/L or females with positive antithyroid antibodies were not associated with pregnancy loss. They concluded from their study that women with borderline thyroid disorders can safely conceive without a risk of pregnancy loss [18]. In our study we took only the pregnant females and when their TSH levels were measured we found a strong positive association of miscarriages in women with raised TSH.

CONCLUSION

It is concluded from our study that there is an increased incidence of miscarriages in females positive for SCH in contrast to females with normal TSH levels. Therefore, this finding therefore highlights the role of antenatal TSH screening to avoid maternal and fetal poor outcome i.e., miscarriages associated with raised TSH levels.

AUTHOR CONTRIBUTION

Beenish Zafar: Manuscript drafting, collection of data, statistical analysis, proof reading.
Ayesha Farooq: Statistical analysis, critical review.
Naveeda Zaigham: Study design, literature review.
Roomisa Anis: Collection of data.
Ayesha Shafaqat: Sample analysis.
Misbah Batool: Data collection, statistical analysis.

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