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Research Article

Association of TSH Level with First Trimester Pregnancy Loss in Anti-TPO Antibody Negative Women in Bangladesh

Yisrat Jahan[1], Enayetur Raheem[2]*, Mohammad Akhteruzzaman[3], M Anwar Hussain[4], Rezaul Karim Kazal[4] and Rifat A. Jahan[5]

[1]*Maternal and Child Health Institute, Bangladesh*
[2]*Deparment of Applied Statistics and Research Methods, University of Northern Colorado, USA*
[3]*Implementation Monitoring and Evaluation Division, Ministry of Planning, Government of Bangladesh*
[4]*Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Bangladesh*
[5]*University of Windsor, Canada*

***Corresponding authors**
Enayetur Raheem, McKee 532, Campus Box 124, University of Northern Colorado, Greeley, CO 80639, USA, Tel: 1-970.351.1644; Fax: 1-970.351.1622; Email: Enayetur.Raheem@unco.edu

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Abstract

Objective: To test if TSH level above 2.1 mIU/L is associated with first trimester pregnancy loss in anti-TPO antibody negative women in Bangladesh.

Study Design: An unmatched case-control study was conducted in Bangladesh. Patients were recruited following predefined inclusion and exclusion criteria. Clinical measures were taken as well as data on socioeconomic and physical characteristics were collected. Patients were grouped according to their TSH level—Group I with TSH ≤2.1 mIU/L and Group II with TSH > 2.1 mIU/L.

Results: We found relatively higher number of women in the case group (18) whose TSH level was above 2.1 mIU/L compared to 7 women in control group. In Group I 45.74% had lost pregnancy while 54.26% had continuing pregnancy during the first trimester. Among the Group II patients, 78% had miscarriage and 28% did not have miscarriage. The association between TSH level and first trimester pregnancy loss was statistically significant (p=.0196).In multivariate analysis, odds ratio for TSH level (OR 4.0, 95% CI: 1.44-11.16) indicates that odds of having miscarriage whose TSH level is above 2.1 mIU/L is 4 times compared to those with TSH level below 2.1 mIU/L after adjusting for the effects of age and BMI.

Conclusion: At a global level, the findings of this study provide evidence to the existing discussion on redefining the upper limit of TSH level that is related to first trimester pregnancy loss. At the local level, the results will have direct implication in facilitating management of future pregnancies particularly during the first trimester among Bangladeshi thyroid autoantibody negative women.

ABBREVIATIONS

TSH: Thyroid Stimulating Hormone; **TPOAb**: *Thyroid Peroxidase Antibody.*

INTRODUCTION

The definition of 'normal TSH level' during pregnancy is changing. Although TSH values of 0.4 to 5.0 mIU/L were considered normal in the past, studies suggest that first trimester TSH values greater than 2.5 mIU/L, and second and third trimester values greater than 3.00 mIU/L are outside the normal range [1]. The decrease in the upper range of TSH level during first trimester of pregnancy may be attributed to the elevation of human chorionic gonadotropin (hCG), which reacts with the TSH receptor causing a decline in the first trimester TSH level [2]. A recent study found TSH level in the first trimester to be negatively

correlated with birth weight of neonates [3]. This also indicates a potential association between TSH level and its impact on first trimester pregnancy loss.

Although the exact level of TSH that is indicative of risk of pregnancy loss is not known, a number of studies have suggested a range of values for TSH level that are associated with first trimester pregnancy loss. For instance, based on a follow up study involving 343 Chinese women, Panesar et al. [4] reported a normal range for first-trimester TSH levels of 0.03–2.3 mIU/L. In a study of 585 thyroid antibody-negative women Pearce et al. [5] found 95% of TSH levels were between 0.04 and 3.6 mIU/L. Study conducted in 1817 Australian women [6], who were between 9 and 13 weeks of gestation reported a normal TSH range of 0.02–2.15 mIU/L. Stricker et al. [7] screened 783 thyroid antibody-negative women from the Geneva, Switzerland area and reported a 95% confidence interval for TSH level to be 0.08–2.83 mIU/L. Although the reported ranges of TSH level to be considered as 'normal' vary, there are consistencies among the study results. There is no agreed upon value of the TSH level, however, a consensus on a lower limit of normal to be 0.04 and upper limit of normal being 2.5 [8].

It is important to consider clinical implications such as pregnancy loss and preterm delivery of untreated cases with first trimester TSH in a range that had previously been considered normal. The increase incidence of pregnancy loss in pregnant women with TSH level between 2.0 and 5.0 mIU/L provides justification to consider investigating the TSH upper limit of normal in the first trimester to a value around 2.0 mIU/L. For the purpose of present study, we chose to evaluate the impact of TSH level above 2.1 mIU/L (high normal) on first trimester pregnancy loss. Of particular interest is to study the socioeconomic determinants that might be associated with first trimester pregnancy loss along with TSH level. Our study involved socioeconomically mid- to well-off women in Dhaka city in Bangladesh. We hypothesize that a TSH value above 2.1 mlU/L may be associated with first trimester pregnancy loss in anti TPO Ab negative women.

MATERIALS AND METHODS

To test our research hypothesis, a cross sectional case control study was conducted where the subjects were selected from out-patient clinics of three centers in Dhaka, Bangladesh. The centers are Department of Obstetrics and Gynaecology under Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka Medical College Hospital (DMCH), and Mohammadpur Fertility Services and Training Centre (MFSTC). After screening for the inclusion and exclusion criteria patients were recruited for the study as they arrived at the facility. Informed written consent was taken from each participant. A predesigned data collection sheet was used to collect data. Ethical clearance for this study was taken from the Institutional Review Board (IRB) of BSMMU.

Inclusion criteria for cases and controls

The case group contained Bangladeshi born anti-TPO Ab negative women between 18-45 years of age, gestational period up to first trimester (12 weeks), and who had recent pregnancy loss which was diagnosed clinically and confirmed by USG. Women in the control group had the similar inclusion criteria but with continuing pregnancy. Anti-TPO Ab level < 35 IU/mL was considered as negative antibody.

Exclusion criteria

Women with the following conditions were not included in the study: pregnancy with known thyroid disease; pregnant women suffering from acute illness such as viral hepatitis, typhoid; those suffering from chronic diseases such as chronic hypertension, chronic renal disease, uncontrolled diabetes mellitus; women who were on medication that interfere with the thyroid function such as steroid, carbamezapine. Further, women who lost pregnancy due to other causes were excluded from the study.

Patients were assigned to case group if they had miscarriage during first trimester. Otherwise, they were assigned to the control group. Subjects were further categorized into two groups according to their TSH level. Group I with TSH level at or below 2.1 mlU/L and those with TSH level above 2.1 mlU/L were in Group II.

Data and variables

After selection of the study subjects, history taking and clinical examination were performed, and diagnosis was confirmed by USG. Medical history, clinical examination results as well as demographic and socioeconomic variables such as patients' age, height, weight, family income, and husband's occupation were collected.

To determine TSH level, 5 ml of venous blood was drawn from ante-cubital vein using disposable syringe with all aseptic precaution. Blood samples were transferred immediately into clean and dry test tubes with gentle push after removal of the needle to avoid hemolysis. The samples were allowed to clot and then centrifuged. Serum was aliquoted into label micro-centrifuged tubes and preserved at 2-8 degree Celsius for future analysis. Analyses of TPO-Ab and TSH were completed using Abott Axsym system/AxSYM 3rd Generation TSH assay within five days of sampling.

Statistical Analysis

Bivariate and multivariate analyses were carried out to the study the association between TSH level and first trimester pregnancy loss. The descriptive results are reported as mean ± SD. Student's 't'-test was performed to test for differences in the means, and Chi-square test was used to test for association between variables. Bivariate results are shown in Tables 1 and 2.

Multivariate analysis was performed to obtain adjusted odds ratios using a binary logistic regression model. For the multivariate analysis, age of patients, BMI, TSH category (≤2.1 mlU/L vs >2.1 mlU/L), and family income (<70,000 Taka/year vs ≥ 70,000 Taka/year) were considered as covariates. Maximum likelihood estimates of the effects and adjusted odds ratios are presented in Table 3.

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Table 1: Cross-tabulation of TSH level and exposure to event (miscarriage).

	Case n (%)	*Control n (%)*	*Chi-square (p-value)*
Group I TSH ≤2.1 mIU/L	43 (45.74) (70.49)	51 (54.26) (87.93)	5.45 (.0196)
Group II TSH >2.1 mIU/L	18 (72.00) (29.51)	7 (28.00) (12.07)	

Figures in each cell represent the counts (first row), row percentage (second row), and column percentage (third row).

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RESULTS AND DISCUSSION

In this study, we had 58 controls and 61 cases. Patients who had a miscarriage within the first trimester were in case group, and who did not have any miscarriage during the first trimester were in the control group. Patients were carefully selected so that the case and control groups are comparable. However, the subjects in case and control groups were not matched. On the basis of serum TSH level, the subjects were further classified as 'low normal' (TSH level up to 2.1 mIU/L) and 'high normal' (TSH level above 2.1 mIU/L). The case and control groups were similar with respect to background characteristics as shown in Table 1. Average ± SD for age (in years) of patients in the case group was 25.06±5.36, and for the control group it was 24.68±5.07. Negro et al. [8] in their study, however, had relatively higher mean age both in the cases and controls (28.7 and 29.2 respectively). Average weight (kg) for case group was 55.45±7.58 and for control group 55.13±6.95. Mean BMI for case group was25.24±6.13, and for the control group it was 24.98±4.31. The two groups were comparable with respect to gestational age (weeks); 8.46 ± 1.88 for the case group and 9.32 ± 2.27 for the control group. We found no statistically significant difference between case and control groups for any of the above mentioned indicators.

RESULTS

The study found the number of women to be relatively higher in Group II (TSH level >2.1 mIU/L) for the cases (18) compared to the controls (7). Among the cases, 29.51% had TSH level above 2.1 mlU/L whereas 12.07% of the control group patients had TSH level above 2.1 mlU/L. When considered patients in Group I (TSH ≤2.1 mlU/L), 45.74% had miscarriage while 54.26% did not have miscarriage. Within the Group II patients, 78% had miscarriage and 28% did not have miscarriage. Noticeably there is a larger proportion of miscarriage among women with TSH level above 2.1 mlU/L. Indeed, the association between TSH level and exposure to event (miscarriage) was statistically significant (Chi-square=5.45, p=.0196).

In bivariate analysis, we found association of TSH level of 2.1 mlU/L with first trimester pregnancy loss. Cross tabulation (Table 2) of family income (below 70,000 Taka/year vs above 70,000 Taka/year) by event status show that in the case group, 55.74% had family income above 70,000 Taka per year (equivalent to USD 900) while the remaining 44.26% had income less than 70,000 Taka per year. Overall, there was no noticeable difference between the case and control groups based on the income categories. We found marginal association (p=.0517) between family income and exposure to miscarriage, which warrants for further investigation through multivariate analysis.

Since univariate or bivariate results do not take into consideration the effects of other factors that might affect the event of interest (miscarriage), we fit a multiple logistic regression model considering age, BMI, family income, and TSH level as covariates. The outcome variable was binary with two categories indicating whether miscarriage occurred or not in the first trimester (see Table 3). We found family income and

Table 2: Cross-tabulation family income and exposure to event (miscarriage).

Family Income	*Case n (%)*	*Control n (%)*	*Chi-square (p-value)*
<70,000 Taka/year	27 (57.14) (44.26)	36 (42.86) (62.07)	3.78 (.0517)
≥70,000 Taka/year	34 (60.71) (55.74)	22 (39.29) (37.93)	

Figures in each cell represent the counts (first row), row percentage (second row), and column percentage (third row).

Table 3: Estimated effects, adjusted odds ratios and 95% confidence intervals for the odds ratios.

Maximum Likelihood Estimates					**Odds Ratio Estimates**		
Parameter	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**	**Point Estimate**	**95% Wald Confidence Limits**	
Intercept	-0.21	1.24	0.03	0.8685			
Age	-0.02	0.04	0.18	0.6688	0.98	0.91	1.06
BMI	-0.002	0.04	0.004	0.9478	0.99	0.93	1.07
TSH level (>2.1)	1.39	0.52	7.05	0.0079	4.01	1.44	11.16
Family Income (≥70,000 Taka/yr)	0.97	0.41	5.70	0.0169	2.64	1.19	5.85

TSH level to be significant predictors of miscarriage. However, age and BMI were not significant. We calculated adjusted odds ratios (OR) for the significant predictors. For TSH level, OR=4.0 with a 95% confidence interval 1.44-11.16 indicates that odds of having miscarriage in women whose TSH level is above 2.1 mlU/L are 4 times compared to women whose TSH level is below 2.1 mlU/L after adjusting for the effects of age and BMI. 95% confidence interval confirms the significance of the estimated odds ratios since the confidence interval do not contain the value 1. Further, adjusted odds ratio for family income (OR 2.64, 95% CI: 1.19-5.85) indicates that adjusted odds of having miscarriage in women whose family income above 70,000 Taka/year are 2.64 times compared to those with lower family income.

DISCUSSION

Results of this study is supportive of the findings of Negro et al. [8] in the sense of redefining the TSH upper limit that is indicative of first trimester pregnancy loss. In Negro et al. [8] they have found significant relationship of TSH level between 2.5-5.0 mlU/L with pregnancy loss. We found TSH level above 2.1 mlU/L to be associated with pregnancy loss. It is to be noted here that our study was different from Negro et al. [8] on several aspects. Most importantly, Negro et al. [8] found smoking to be a significant predictor which we did not consider in our study since smoking is generally uncommon among Bangladeshi women.

The general conclusion of our study that TSH is associated with first trimester pregnancy loss is in conformity with other studies that dealt with evaluating the association between hypothyroidism and first trimester spontaneous miscarriages [9]. Results that are similar to the findings of this study include the work of Panesar et al. [4] who reported a normal range for first-trimester TSH levels of 0.03–2.3 mIU/L; that of Gilbert et al. [6], who found a normal TSH range of 0.02–2.15 mIU/L; and that of Stricker et al. [7] who reported a 95% confidence interval for normal TSH level to be 0.08–2.83 mIU/L. Similar to these studies, our cut-off point for the normal TSH level (2.1 mlU/L) is close to the upper limits suggested in these studies.

There have been many studies involving women in different parts of the world to study the association between TSH level and first trimester pregnancy loss. But, to the best of our knowledge, there was no such study involving Bangladeshi women to determine the TSH level that is indicative of first trimester pregnancy loss. As such, part of our objective was to determine the TSH level that is indicative of the significant first trimester pregnancy loss in addition to verifying the existing bound, which is > 2.5 mlU/L. We consider several cutoff points in the multivariate analysis. In particular, we found that there are statistically significant odds ratios for cutoff points 2.0, 2.1, and 2.2.

Given that we have several candidate cutoff points, we then considered percentage of women who are above these threshold levels. We found the 75th percentile point was for TSH level 2.04, 80th percentile point was for TSH level 2.2. We therefore, choose level 2.1 which is closer to the 75th percentile. This indicates that 25% of the women in this study had TSH level above 2.1 mlU/L. Considering all these factors, we decided TSH level of 2.1mlU/L to be a conservative value above which a significant proportion of miscarriage occurs among the study subjects. It is worth mentioning that any value between 2.0 and 2.2 could have been chosen and our conclusion would have remained the same based on multivariate analysis.

Based on the reviewed literature, we reiterate that there is no agreed upon value for the upper limit of normal TSH level that is associated with first trimester pregnancy loss. Recent literature have suggested to lower the upper limit, and considered ongoing research to redefine the limit as a “scientific debate” [8,10].

CONCLUSION

It is well documented in the reviewed literature that TSH level has significant effect on the first trimester pregnancy loss among the thyroid autoantibody negative women. However, the upper limit varies across different demographic characteristics of women. Proper maternal thyroid function during pregnancy is important for both the mother and the developing fetus. This is particularly true during the first trimester, when the fetus is completely dependent on the mother for thyroid hormone. This study detects significant relationship between high normal TSH (>2.1 mlU/L) and miscarriage in first trimester among mid- to well-off women whose family income is above 70,000 Taka/year. At a global level, our findings provide evidence to the existing discussion on redefining the upper limit of TSH level that is related to first trimester pregnancy loss. At the local level, the study results will have direct implication in facilitating management of future pregnancies particularly during the first trimester among Bangladeshi thyroid autoantibody negative women.

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