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Original Article

Biochemistry Section

Association between Thyroid Function and Ovarian Reserve in Infertile Women: A Cross-sectional Study

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ABSTRACT

Introduction: Thyroid dysfunctions are among the most common diseases in women of reproductive age group. Thyroid hormone receptors are present on oocytes which indicate that thyroid hormones may influence ovarian functions. Serum Anti-Müllerian Hormone (AMH) is secreted from growing granulosa cells of ovaries. Serum AMH concentrations are used to evaluate ovarian reserve in females.

Aim: To find the association between ovarian reserve, measured by AMH concentration and thyroid functions in women with infertility.

Materials and Methods: This cross-sectional study was conducted on a total of 78 infertile females, in Department of Biochemistry at Government Medical College, Badaun, Uttar Pradesh, India, from July 2021 to December 2021. The involved women with infertility in the age group of 20-40 years attending the infertility clinic, were included in the study. Participants were divided into two groups based on whether the serum AMH value was <1 ng/mL (lower than low normal ovarian reserve) or ≥1 ng/mL (low normal to normal ovarian reserve). The blood samples were processed for Serum Thyroid Stimulating Hormone (TSH), free Triiodothyronine (fT_3), free Thyroxine (fT4), Prolactin and AMH. The median values of TSH and fT4 levels were compared in the subgroups of patients defined by the level of serum AMH i.e., serum AMH value <1 ng/mL, and serum AMH value ≥1 ng/mL. Chi-square test was used to establish the association between the categorical variables.

Results: Based on serum AMH values, 22 (28%) females had below normal ovarian reserve i.e., serum AMH value <1 ng/mL, and 56 (72%) females had low normal to normal ovarian reserve i.e., serum AMH value ≥1 ng/mL. The mean age of participants with AMH <1 ng/mL was 33.23±4.28, which was significantly higher than those with AMH value ≥1 ng/mL (p-value=0.002). Serum TSH value was significantly higher in the subgroup of participants with AMH <1 ng/mL, the value being 4.75 mIU/L and was lower (2.8 mIU/L) in the subgroup of participants with AMH ≥1 ng/mL (p-value=0.002).

Conclusion: In conclusion, the present study found the highly significant difference in serum TSH values in the two groups based on whether the serum AMH value was <1 ng/mL and ≥1 ng/mL suggesting that subclinical hypothyroidism has negative impact on the female fertility. Increasing age of the females was negatively correlated with the ovarian reserve.

Keywords: Anti-müllerian hormone, Free thyroxine, Hypothyroidism, Reproductive age, Thyroid stimulating hormone

INTRODUCTION

A couple, who is unable to achieve pregnancy over an average period of one year (in women under 35 years of age) or six months (in women above 35 years of age) of unprotected sexual intercourse, is termed as infertile. Infertility can be due to female or male or both reasons. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a couple, and secondary infertility is when atleast one prior pregnancy has been achieved [1].

Thyroid dysfunctions are among the most common diseases in women of reproductive age group [2-4]. Thyroid hormone receptors are present on oocytes that indicate thyroid hormones may influence ovarian functions. It is well-established fact that the menstrual cycle is prolonged in females of hypothyroidism and may lead to infertility because of altered peripheral oestrogen metabolism, hyperprolactinaemia and abnormal release of gonadotropin-releasing hormone [5].

Anti-Müllerian Hormone (AMH) is a dimeric glycoprotein which belongs to the Transforming Growth Factor-beta (TGF-β) super family. AMH acts on tissue growth and differentiation. AMH is produced by the granulosa cells from pre-antral and small antral follicles [6]. Serum AMH concentrations are used to evaluate ovarian reserve in females and can be used as a good marker for ovarian reserve [7-9]. Concentration of AMH tends to decrease with age [10]. A number of studies support the association between high serum TSH level and decreased ovarian reserve [11,12].

Thus, the aim of the present study was to find the association between ovarian reserve, measured by AMH concentration and thyroid functions in women with infertility.

MATERIALS AND METHODS

This cross-sectional study was conducted in Department of Biochemistry at Government Medical College, Badaun, Uttar Pradesh, India, from July 2021 to December 2021. The involved women with infertility in the age group of 20-40 years attending the infertility clinic. The ethical clearance was obtained from the concerned Institutional authority (Dated:16/9/2022) and written informed consent was taken from the patients who were enrolled in study.

Sample size calculation: The prevalence of hypothyroidism among women with infertility was found to be 53.7% [13]. Considering the absolute margin of error to be 12.5%, the minimum required sample size for undertaking a cross-sectional study (openepi.com) came out to be 62. A total of 118 females were recruited for the study. After exclusion, 78 participants were enrolled in the study.

Inclusion and Exclusion criteria: Women with infertility in age group of 20-40 years, who gave consent to participate were included in the study. Women with other causes of infertility i.e, partner infertility, Polycystic Ovary Syndrome (PCOS), hyperprolactinemia, tubal blockage, ovarian surgery and on treatment for hypothyroidism were excluded from the study.

Systematic random sampling was used to recruit the participants attending the infertility clinic at a tertiary care facility in Badaun. Data

was collected two days a week for six months. Every third patient attending the clinic was enrolled in the study starting from any random patient. If the patient was not willing to participate, the third patient starting from her was enrolled, if willing. A maximum of three such patients were enrolled on each day when data was collected.

Study Procedure

Total 118 patients were then subjected to a proforma regarding the demographic details (like age, the period since marriage, the period since the couple has been trying to conceive) and clinical features. Nine patients were excluded based on evidence of their partner's infertility. Thirteen patients were later diagnosed with having PCOD and hence, excluded from the study.

The blood sample was drawn from the remaining 96 participants. The sample was processed for Serum Thyroid Stimulating Hormone (TSH), free Triiodothyronine (fT_3), free Thyroxine (fT_4), Prolactin and Anti-Müllerian Hormone (AMH). Elecsys® technology and Cobas e411 analyser (Electrochemiluminescence immunoassay) was used for the quantitative determination of the hormones in human serum [14]. Hyperprolactinaemia was observed in 16 samples and hence, they were excluded from the study. On data entry, two values of AMH were identified as outliers and excluded. Test result values of 78 patients were thus, included in the data analysis.

In subclinical hypothyroidism, the TSH is minimally increased while the free T4 stays within the normal range. In subclinical hypothyroidism the serum TSH value of more than 4.2 mIU/L with normal free T4 value between 12-22 pmol/L and in clinical hypothyroidism serum TSH value of more than 4.2 mIU/L with decreased free T4 value less than 12 pmol/L were considered [15-17]. [Table/Fig-1] shows the reference ranges for various parameters used in the study [16-22].

Parameters	Reference range (Female)
Thyroid Stimulating Hormone (TSH)	0.5-4.2 mIU/L
Free Thyroxine (fT_4)	12-22 pmol/L
Free Triiodothyronine (fT_3)	3.1-6.8 pmol/L
Prolactin	102-496 µIU/mL
Anti-Müllerian Hormone (AMH)	Normal: 1-4 ng/mL Low: <1 ng/mL

[Table/Fig-1]: Reference ranges for various parameters used in the study [16-22].

STATISTICAL ANALYSIS

Data was entered and analysed using the software Statistical Package for Social Sciences (SPSS) version 23.0. The normality of data distribution was evaluated using the Shapiro-Wilk's Test of Normality. As the values of TSH and fT_4 were not distributed normally, the Independent sample Kruskal-Wallis test was used to compare the median values of TSH and fT_4 levels in the mentioned subgroups of patients. The Chi-square test was used to establish the association between the categorical variables. Where more than one cell showed a value <5 (in 2×2 tables), Fisher's-Exact test was used. A p-value of <0.05 was considered significant. The Pearson's correlation test was used to establish the linear relationship between the variables (TSH and AMH levels). Bivariate regression analysis was used to identify the strength of association between continuous independent variables (age and TSH levels) and the dichotomous dependent variable of whether the female had lower than low normal serum AMH levels. The same test was used to identify the strength of association between the dichotomous independent variable of whether hypothyroidism was present, with the outcome. Multiple regression analysis was used to identify the independent predictors for having lower than low-normal ovarian reserve in women with infertility.

RESULTS

A total of 78 infertile females were included in the study. The mean age of the participants was 30.59±4.67 years. Based on serum AMH values, 22 (28%) females had below normal ovarian reserve i.e., serum AMH value <1 ng/mL, and 56 (72%) females had low normal to normal ovarian reserve i.e., serum AMH value ≥1 ng/mL.

[Table/Fig-2] shows that most of the participants were in the age group of 26 to 30 years. The proportion of females with AMH <1 ng/mL was maximum (36.4%) in the age group of 36 to 40 years and was minimum in the age group 20-25 years. An ascending trend was observed, with a higher proportion of infertile females with lower than low normal ovarian reserve falling in older age groups. The association was found to be statistically significant. The mean age of participants with AMH <1 ng/mL was 33.23±4.28, which was significantly higher than those with AMH value ≥1 ng/mL.

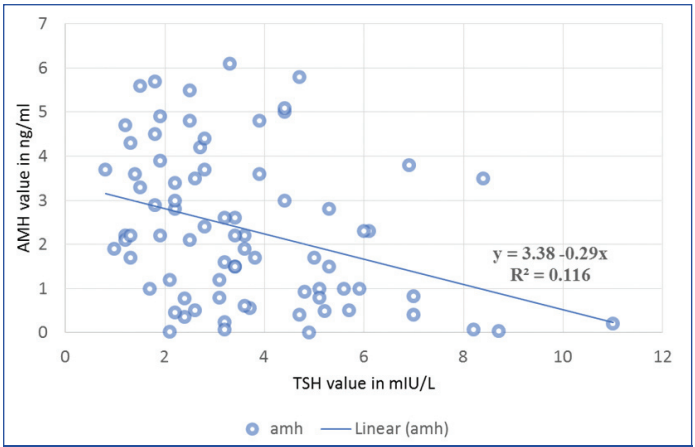
Parameters	AMH <1 ng/mL (n, %) (N=22)	AMH ≥1 ng/mL (n, %) (N=56)	Total (n, %) (N=78)	p-value
Age (years)				
20 to 25	1 (4.5%)	13 (23.2%)	14 (17.9%)	0.023*
26 to 30	6 (27.3%)	23 (41.1%)	29 (37.2%)	
31 to 35	7 (31.8%)	14 (25%)	21 (26.9%)	
36 to 40	8 (36.4%)	6 (10.7%)	14 (17.9%)	
Mean age (Mean±SD)	33.23±4.28	29.55±4.44	30.59±4.67	0.002#
Hypothyroidism				
Yes	11 (50%)	9 (16.1%)	20 (25.6%)	0.002*
No	11 (50%)	47 (83.9%)	58 (74.4%)	
Clinical hypothyroidism				
Yes	4 (18.2%)	2 (3.6%)	6 (7.7%)	0.050**
No	18 (81.8%)	54 (96.4%)	72 (92.3%)	
Subclinical hypothyroidism				
Yes	7 (31.8%)	7 (12.5%)	14 (17.9%)	0.045*
No	15 (68.2%)	49 (87.5%)	64 (82.1%)	
Serum levels	**Median value (IQR)**			
TSH (mIU/L)	4.75 (2.98-6.18)	2.8 (1.8-3.9)	3.2 (2.1-4.83)	0.002##
fT4 (pmol/L)	16.6 (13.63-18.78)	17.05 (15.53-18.50)	17.05 (15.53-18.55)	0.262##

[Table/Fig-2]: Quantitative variables based on participants' AMH value.
IQR: Interquartile range; *Chi-square test, **Fisher's-Exact Test, #Independent Sample T-test, ##Independent Sample Kruskal-Wallis Test

While a quarter of the total sample was found to have hypothyroidism, about half of those with AMH <1 ng/mL had hypothyroidism as compared to only about 16.0% of those with AMH ≥1 ng/mL. This association was found to be highly significant statistically (p-value=0.002). The median TSH value for the study population was 3.2 mIU/L lying within the interquartile range of 2.1 to 4.83. This value was significantly higher in the subgroup of participants with AMH <1 ng/mL, the value being 4.75 mIU/L and was lower (2.8 mIU/L) in the subgroup of participants with AMH ≥1 ng/mL [Table/Fig-2].

It can be seen from [Table/Fig-3] that TSH values and AMH values were related negatively with each other. With a unit rise in TSH values, the AMH value tends to fall by 0.29 units. A 11.6% variance in the AMH values can be attributed to TSH values. [Table/Fig-4] shows that the serum TSH value of participants was negatively correlated with AMH values. So, with a rise in TSH value, the AMH value is supposed to fall. The two variables are weakly correlated, with the value of Pearson's correlation coefficient=0.341. The relationship was found to be statistically highly significant. A similar relation was seen between age and AMH values with the coefficient=0.346. No significant correlation was present between the variables of age and TSH levels in infertile women.

On bivariate regression analysis, it was concluded that with a unit rise in serum TSH value, the odds of having AMH value of less than 1 ng/mL increases by 1.57, with a 95% confidence interval of 1.13



[Table/Fig-3]: Scatter showing relationship between serum TSH and AMH levels of the participants.

The association between serum TSH and AMH levels was found to be highly significant. In the study, conducted by Kabodmehri R et al., inverse relationship between serum TSH levels and ovarian reserve has been observed. they concluded that an increase in TSH from a cut-off point of 1.465 mIU/L in participants over the age of 35 years, is associated with a decrease in ovarian function [20]. The study conducted by Sammour HM et al., also concluded that elevated serum TSH is associated with decreased serum AMH in infertile women of reproductive age [24].

Michalakis KG et al., have also shown an association between serum TSH levels and ovarian reserve, and in 18% of patients with low ovarian reserve, TSH levels were higher than 4 µIU/mL [24].

The association between serum TSH and AMH levels have been suggested even in euthyroid patients as the serum TSH levels <3 mIU/mL are associated with better ovarian function and if TSH is higher than this value, they recommended levothyroxine treatment [11,25].

Variables	Median value (IQR) in participants with AMH <1 ng/mL	Median value (IQR) in participants with AMH ≥1 ng/mL)	p-value	Pearson's correlation coefficient	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
TSH	4.75 (2.98-6.18)	2.8 (1.8-3.9)	0.002	-0.341*	1.57 (1.13-2.19)	1.61 (1.17-2.21)
Age	33.23±4.28	29.55±4.44	0.002	-0.346*	1.2 (1.06-1.35)	1.17 (1.06-1.39)
Variables	**Participants with AMH <1 ng/mL**	**Participants with AMH ≥1 ng/mL**	**p-value**	**Adjusted odds ratio (95% CI)**		
Hypothyroidism	11 (50%)	9 (16.1%)	0.002	5.67 (1.71-18.88).		

[Table/Fig-4]: Correlation, bivariate and multivariate regression analysis between continuous quantitative variables based on participants' AMH levels.
IQR: Inter quartile range, C.I: Confidence interval; * Correlation is significant at the level of 0.01

to 2.19. Similarly with a unit increase in age, the odds of having AMH value <1 ng/mL increases by 1.2 with 95% confidence interval being 1.06-1.35 [Table/Fig-4]. After accounting for confounding factors by multiple regression, both the variables continue to predict the outcome independently, thus, the association between the serum TSH levels and low ovarian reserve is independent of whatever association age and serum TSH levels may have with each other. The adjusted Odds Ratio (aOr), hence obtained can be seen in [Table/Fig-4].

It can also be seen from [Table/Fig-4], that when TSH values are converted to binomial variable of whether hypothyroidism is present or not, the presence of hypothyroidism (adjusted for confounding by age) comes out to be a stronger independent predictor of having AMH value less than 1 ng/mL with adjusted Odds Ratios (aOR) (95% confidence interval) being 5.67 (1.71-18.88).

DISCUSSION

In the present study, serum TSH values and AMH values were negatively related with each other. The infertile females with low AMH values had significantly higher values of serum TSH than the females with normal AMH values, showing that the higher values of serum TSH have directly effect on female fertility.

In the present study, the association between serum TSH and fT_4 levels and serum AMH as a marker of ovarian reserve in infertile females was examined. Ascending trend was observed, with a higher proportion of infertile females with lower than the low normal ovarian reserve falling in older age groups that was found to be statistically significant. The mean age of participants with AMH <1 ng/mL was 33.23±4.28, which was significantly higher than those with AMH value ≥1 ng/mL (29.5±4.44). This was similar to the study conducted by van Rooij IA et al., that suggest that the concentration of AMH tends to decrease with age [10]. Study conducted by Gougeon A et al., showed that decrease in ovarian reserve and its acceleration at the age of 37.5 years [23]. The results of present study are also in concordance with the study performed by Krassas G et al., that showed the statistically significant difference between the infertile women and the normal fertile women with regard to the age [5].

Kucukler FK et al., found no significant difference between patients with overt or subclinical hypothyroidism and control group in regard to ovarian reserves measured by serum AMH concentration and total antral follicle count. However, lower serum AMH concentration was present in overt and subclinical hypothyroidism patient in their study and they suggested for close follow-up of these patients [26]. The current study findings contradict with a number of other studies. A study conducted by Wu J et al., found no significant correlation between the ovarian reserve and thyroid function-related indicators in women with infertility [27]. A cross-sectional analytical study by Polyzos NP et al., was conducted in a cohort, all three groups of patients with normal, low, and high ovarian response were included [28]. Polyzos NP et al., found no significant correlation between serum TSH and AMH levels and their results were supported by the findings of several other studies [28-30].

Since, the higher values of serum TSH have direct negative effect on female fertility, it should be addressed as a cause when considering the treatment for infertility in females.

Limitation(s)

Limitations of the present were the inability to evaluate antithyroid antibodies to see the effect of thyroid auto-immunity on ovarian function. Further studies can be done with the evaluation antithyroid antibodies in future.

CONCLUSION(S)

Significant difference was observed among serum TSH values in the two groups based on whether the serum AMH value was less than 1 ng/mL and equal to or more than 1 ng/mL. The study suggests that the subclinical hypothyroidism has negative impact on the female fertility and increasing age of the females is negatively correlated with the ovarian reserve.

Authors' contributions: SC contributed to conception and study design. SSS did data collection, drafted the manuscript and revised it. SS performed statistical analysis. All authors read and approved the final manuscript.

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