

A Retrospective Study to Evaluate the Correlation of Thyroid Stimulating Hormone and Anti Mullerian Hormone as Contributors to Infertility in Females of Reproductive Age Group.

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Abstract

Thyroid dysfunction is a common endocrine disorder and has been identified to adversely impact the fertility outcome in women. In particular, overt and subclinical hypothyroidism may lead to menstrual irregularities and anovulation and has been associated with increased risk of infertility because of altered peripheral oestrogen metabolism, hyperprolactinaemia and abnormal release of gonadotropin-releasing hormone. It has also been suggested that thyroid dysfunction might impair follicular growth and maturation. Anti-Müllerian hormone is a dimeric glycoprotein belonging to the transforming growth factor-β super family. It is produced by the granulosa cells of early developing follicles and has been linked to the number of small follicles, hence the reserve of the ovaries, Anti-Müllerian hormone is thus a suitable biomarker of ovarian age in women. However, how thyroid function affects ovarian function has not been elucidated till date.

Introduction

Thyroid dysfunction is a common endocrine disorder and has been identified to adversely impact the fertility outcome in women. In particular, overt and subclinical hypothyroidism may lead to menstrual irregularities and anovulation [1] and has been associated with increased risk of infertility [2] because of altered peripheral oestrogen metabolism, hyperprolactinaemia and abnormal release of gonadotropin-releasing hormone [3]. It has also been suggested that thyroid dysfunction might impair follicular growth and maturation [4]. Michalakakis KG et al [5] reported an elevated serum Thyroid Stimulating Hormone levels (further being referred to as TSH) which was associated with diminished ovarian reserve in infertile patients. Reports also suggest that thyroxine supplementation may improve fertility, in particular, implantation and miscarriage rates, leading to successful pregnancy [6-7].

Anti-Müllerian hormone (further being referred to as

AMH) is a dimeric glycoprotein belonging to the transforming growth factor-β superfamily. It is produced by the granulosa cells of early developing follicles and has been linked to the number of small follicles, hence the reserve of the ovaries [8-10], AMH is thus a suitable biomarker of ovarian age in women [11]. However, how thyroid function affects ovarian function has not been elucidated till date.

This study was designed to evaluate the relationship between thyroid function and AMH levels by comparing them in women of different age groups seeking treatment for infertility.

Materials and Methods

The study involved data retrieval and retrospective review of medical records of 100 women of different age groups who had failed to conceive and were undergoing workup prior to seeking treatment for infertility. Infertility is defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Analysis of data was carried out maintaining full confidentiality of patient's medical records along with protection of patient's identity.

The tests were performed on samples collected from patients on day 3 of menstrual cycle in the Department of Biochemistry and Department of Serology between June

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Received: 29-02-2020

Accepted: 03-04-2020

2018 to November 2018. TSH was assayed in serum, using standard commercial third generation chemiluminescence immunoassay, with reference values of 0.40-4.50 mIU/L as normal range. AMH levels were assessed by manual Enzyme-Linked Immunosorbent Assay (ELISA) using standard kits, with a normal reference range of 2.20-6.80 ng/ml. Besides AMH and TSH, FSH, LH, Estradiol, Total testosterone and Prolactin were also measured using commercially available chemiluminescence immunoassay.

Patients with factors that adversely impact thyroid hormone and ovarian function, as derived from patient history sheet, were excluded from the study (ovarian tumor, ovarian surgery, endometriosis, history of smoking). Patients over 40 years of age were excluded from the study. Only newly diagnosed cases with thyroid abnormality as indicated by deranged TSH level and absence of medication history for thyroid illness were included in the study. The study population included patients in the age group of 20-39 years.

To investigate the relationship between thyroid function (TSH) and serum AMH levels, the study population was divided age wise into four groups - ≤ 25 years (mean age 22.5 ± 2.12 years), 26-30 years mean age 28.3 ± 1.49 years), 31-35 years (mean age 32.9 ± 1.32 years) and 36-39 years (mean age 37.5 ± 1.50 years). Data was analyzed using SPSS (Statistical Package for Social Sciences) software, Version 20 and results were expressed as mean \pm SD. Correlation coefficient (r) between TSH and AMH was calculated to measure the strength of relationship between the two variables. Correlation study was also done between the patients with low AMH levels and their respective ages to figure out the association. A probability (p) value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics of the infertile patients are given in Table 1.

Out of the 100 infertile women enrolled into the study, 38 had low AMH levels.

Age-wise distribution of the 38 patients' having low AMH levels is depicted in the Table 2.

25 among 38 women had high TSH levels with low AMH levels. Correlation analysis between TSH and AMH levels in women with low AMH was done to figure out the relationship between the two variables. Statistical analysis revealed a negative correlation (correlation coefficient $r = -0.3273$) between AMH and TSH with a p value of 0.0449, considered significant.

A negative correlation (correlation coefficient $r = -0.3914$) was also obtained for AMH and ages of the study population with a p value of <0.0001 , considered extremely significant.

Discussion

Thyroid hormones have profound effects on reproduction and pregnancy and has been associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and infertility [14,15]. The association between low ovarian reserve as a cause of infertility and deranged thyroid function is still under evaluation. This study was attempted to envisage correlation between thyroid function as indicated by the TSH levels of the study population and ovarian reserve as depicted by AMH levels.

The mean age of the patients enrolled in the study was 30.07 ± 5.55 years. 25% of the cases enrolled into the study reported low AMH and high TSH levels which was

Table 1: Baseline Characteristics of the Infertile Patients

	≤ 25 years	26-30 years	31-35 years	36-39 years
Number of patients in each age group	25	23	34	18
Mean AMH in ng/ml	5.95 ± 4.96	4.64 ± 3.16	2.46 ± 1.72	2.02 ± 2.55
Mean TSH in mIU/L	4.25 ± 5.01	4.29 ± 4.02	6.76 ± 12.03	8.76 ± 7.96

Table 2: Age Wise Distribution of the patients' having low AMH levels

	≤ 25 years	26-30 years	31-35 years	36-39 years
Number of patients having low AMH levels in each age group	6	5	14	13

found to be statistically significant with a p value of 0.0449. This data revealed a negative correlation between TSH and AMH levels in infertile women with diminished ovarian function without other factors affecting thyroid and ovarian function. This finding has been consistently reported by previous studies [3, 12]. Thus, TSH may be a factor influencing ovarian reserve in infertile patients.

This study also revealed significant statistical difference ($p < 0.0001$) between AMH level and patient's age, which is in agreement with other studies [16]. Literature data has shown AMH as the most accurate marker of the growing follicle pool and therefore, of ovarian function [16]. These studies have also reported that higher AMH concentrations are associated with larger oocyte yields and improved pregnancy potential.

Hypothyroidism is associated with increased production of TRH, which stimulates pituitary to secrete TSH and PRL. Hyperprolactinemia consecutively has adverse effects on the fertility potential by causing impaired GnRH pulsatility and thereby ovarian function [17].

Previous studies have reported subclinical hypothyroidism as a primary cause of subfertility, with a prevalence of 20% in infertile women [18, 19]. A recent meta-analysis by Velkeniers et al established that thyroxine treatment in women with subclinical hypothyroidism and/or thyroid autoimmunity increases chances of fertilization, implantation and live birth rate in women undertaking assisted reproduction [7]. Moreover, thyroid hormone has been implicated to play a significant role in follicular development [20, 21]. In addition, TSH directly suppressed follicle development in a concentration-dependent manner [22].

Conclusion

The study reported statistically significant negative correlation between TSH and AMH levels suggesting that ovarian reserve is affected by impaired thyroid function. Infertility has a significant medical, economical and psychological implications in our society. The findings of the study may thereby influence the infertility treatment strategies, aiding in the choice of right modality of treatment.

The study is however not free of limitations. First, the study was a single centre study. Secondly, significant data on autoimmune thyroid antibodies could not be obtained which is also believed to be strongly associated with the fertility outcome.

For better management of infertility, multi centre studies with large sample size with longer term of follow up is recommended to validate the variation in TSH and monitor treatment outcomes. A prospective study of

thyroxine therapy for patients with decreased AMH and increased TSH levels is also warranted in future.

Conflict of interest:	All authors declare no COI
Ethics:	There is no ethical violation as it is based on voluntary anonymous interviews
Funding:	No external funding
Guarantor:	Dr Malvika Srivastava will act as guarantor of this article on behalf of all co-authors.

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