Original Article

DOI: 10.7860/JCDR/2022/58369.17072

Evaluation of Ovarian Reserve among Newly Diagnosed Hashimoto's Thyroiditis Related Subclinical and Overt Hypothyroid Reproductive Women: A Cross-sectional Study

Biochemistry Section

AKINEPALLI PULLAIAH[1], VEERENDRA KUMAR ARUMALLA[2]

ABSTRACT

Introduction: Thyroid autoimmunity is a common autoimmune disorder among reproductive women. It is proposed that, thyroid peroxidase antibodies pass through the blood follicle barrier during follicular development which damages the growing follicles and oocytes. Previous studies have demonstrated the association between thyroid autoimmunity and ovarian failure. Serum Anti-Müllerian Hormone (AMH) levels are used as a marker of ovarian reserve in clinical practice.

Aim: To evaluate ovarian reserve among newly diagnosed Hashimoto's Thyroiditis (HT) related subclinical and overt hypothyroid women.

Materials and Methods: A cross-sectional study was conducted at the Department of Biochemistry, Government Medical College Nalgonda, Telangana, India, from August 2020 to July 2021. The study included 180 subjects, 60 in each Overt Hypothyroid (EU group) (OH group), Subclinical Hypothyroid (SCH group) and Euthyroid subjects. Socio-demographic details and other parameters age, Body Mass Index (BMI), AMH, Thyroid Stimulating Hormone (TSH), free T4 (fT4), Thyroid Peroxidase Antibodies (TPOAb), Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Antral Follicular Count (AFC) were evaluated and compared in all the three groups. The above data were recorded and analysed using Statistical Package for Social Sciences (SPSS) version 20.0 and the Analysis of Variance (ANOVA) test, Chi-square test, and Spearman's correlation test were performed for statistical analysis.

Results: The median age, BMI, and total AFC were not statistically significant (p-value >0.05). Serum TPOAb levels were significantly (p-value <0.001) high in the OH group and SCH group when compared to the EU group. The AMH levels were significantly (p-value=0.015) high in the EU group compared to the OH group, but there were no statistically significant differences among other groups. The AMH values were negatively correlated with age among all the three groups. There was no significant correlation between AMH and other parameters analysed among different groups.

Conclusion: The AMH levels were significantly low in the OH group when compared to the EU group. There were no statistically significant differences among other groups. Age was found to be an independent factor for low AMH levels among all the three groups.

Keywords: Anti-müllerian hormone, Thyroid autoimmunity, Thyroid stimulating hormone, Thyroid peroxidase antibodies

INTRODUCTION

Autoimmune Thyroid Disease (AITD) is the most common endocrine disease among women of reproductive age. Its prevalence was reported to range from 5% to 15% [1]. Hypothyroidism is associated with menstrual irregularities and infertility.Severe hypothyroidism is commonly associated with ovulatory dysfunction due to numerous interactions of thyroid hormones with the female reproductive system. Thyroid responsivity by the ovaries could be explained by the presence of thyroid hormone receptors in human oocytes [2]. The pathophysiology of how Autoimmune Thyroid Disease (AITD) reduces ovarian reserve has not been well established. Given that thyroxin discovered in human follicular fluid is important for oocyte development and AITD decreases thyroid function by disturbing the hypothalamus pituitary gonadal axis, AITD may decrease ovarian reserve by affecting endocrinology [3]. Secondly, antithyroid peroxidase antibodies may activate an immune reaction to damage the ovarian tissue because antithyroid antibodies are also detected in ovarian follicles [4,5].

It is well known that a prolonged reduction in thyroid hormone concentration results in a broad spectrum of reproductive alteration, including abnormal folliculogenesis, alterations in the ovulation and fertilisation rate, and ovarian failure [6-8]. In clinical practice, hormonal markers like Follicle Stimulating Hormone (FSH), Estradiol (E2), Anti-Müllerian Hormone (AMH), and ultrasound parameter Antral Follicle Count (AFC) are used for evaluating ovarian reserve. Anti-müllerian hormone is produced by the granulosa cells of ovarian antral follicles. AMH concentrations show a significant correlation with oocyte count after superovulation and can be used as a good marker for evaluating ovarian reserve [9]. Previous studies showed varying results on the association between TSH, Thyroid Peroxidase Antibodies (TPOAb), and AMH (ovarian reserve). A study conducted by Ozturkunsal I et al., showed no significant correlation between AMH concentrations with the serum levels of TPOAb and TSH [10]. Chen CW et al., showed positive TPOAb was associated with low ovarian reserve [11]. Another study by Osuka S et al., showed that TPOAb is not likely to affect ovarian reserve in euthyroid women with normal TSH, but elevated TSH is associated with decreased AMH levels [12]. Studies conducted by Polyzos NP et al., Korevaar TIM et al., Kucukler FK et al., and Morales Martínez FA et al., showed no relationship between thyroid hormone levels and AMH levels [13-16].

As the earlier studies showed varying results on how ovarian reserve was affected by thyroid autoimmunity, the present study aimed to evaluate ovarian reserve among newly diagnosed Hashimoto's thyroiditis related subclinical and overt hypothyroid women using serum AMH levels and other relevant markers. The authors also aimed to find out the possible correlation between thyroid hormone status, thyroid autoantibodies, and AMH levels in the study subjects.

MATERIALS AND METHODS

A cross-sectional study was conducted at the Department of

Biochemistry, Government Medical College Nalgonda, Telangana, India, from August 2020 to July 2021. The study was approved by Institutional Ethical Committee (No: IEC/GMC/06-2020). Written Informed consent was obtained from all the subjects.

Sample size calculation: From a previous study with an alpha error of 5% and power of 80%, required sample size was 168 [15]. The sample size was calculated by using MedCalc statistical software version 20.0. Total of 180 women aged between 20-40 years were enrolled in the present study, with 60 subjects in each group.

- Newly diagnosed Hashimoto's Thyroiditis (HT) patients with Overt Hypothyroid (OH) (n=60).
- Newly diagnosed HT patients with Subclinical Hypothyroid (SCH) (n=60).
- Healthy subjects with Euthyroid (EU) (n=60).

Inclusion criteria: Newly diagnosed Hashimoto's Thyroiditis patients with OH and SCH who were attending General Medicine and Gynaecology Departments were included in the study, and healthy subjects with euthyroid were involved as the control group.

Exclusion criteria: Patients with thyroidectomy, thyroid treatment, polycystic ovarian syndrome, endometriosis, and history of ovarian surgery, patients on radiotherapy, chemotherapy, and diabetic subjects were excluded from the study.

Diagnosis of Hashimoto's thyroiditis was made when patients have high levels of antithyroid antibodies and parenchymal heterogeneity on ultrasonography of the thyroid gland [15]. Increased TSH levels >10 μIU/mL together with low free T4 (fT4) were considered overt hypothyroidism and mildly increased TSH levels (4.2-10 μIU/mL) in the presence of normal free T3 (fT3) and fT4 values were regarded as subclinical hypothyroidism. Euthyroid was defined as patients with normal thyroid function tests [15].

Study Procedure

Venous blood samples were collected between the third to sixth days of the menstrual cycle from all the subjects. Serum was separated from whole blood and samples were stored at -20°C until an assay was performed. The TSH, fT4, TPOAb, FSH, Luteinizing Hormone (LH), E2, and AMH were measured on the Beckman Coulter – Access 2 Immunoassay System using the Chemiluminescence Immunoassay (CLIA) method with Beckman Coulter commercial kits. The AMH concentration <1 ng/mL was considered as low. Reference ranges for TSH (0.34-5.6μIU/mL), fT4 (0.58-2.19 ng/dL), TPOAb (0.0-9.0 IU/mL), FSH (1.85-8.78 mIU/mL), LH (2.12-10.89 mIU/mL), E2 (26.5-161.3 pg/mL). These reference values were as given in the kit inserts used in the laboratory for assay. On the same morning as the blood tests, transvaginal ultrasonography evaluation of the Antral Follicle Count (AFC) was performed with a MINDRAY DC-7 model ultrasonography device in the lithotomy position. Antral follicles with a diameter of 2-10 mm were counted. Thyroid gland ultrasonography was performed using Philips ClearVue 650 ultrasound machine by an endocrinologist.

STATISTICAL ANALYSIS

Kolmogorov-Smirnov test was used to check the normal distribution of the quantitative variables. Descriptive statistics were presented as median and interquartile ranges (25^{th}-75^{th} percentile) for non normally distributed parameters. The Analysis of Variance (ANOVA) test or Kruskal-Wallis test were used to evaluate the significance of the mean difference between more than two groups where applicable. To find out the correlation between two continuous variables, Spearman's correlation test was used. Linear regression analysis was performed to test the influence of independent variables on AMH levels (dependent variable). Statistical Package for the Social Sciences (SPSS) for windows version 21.0; (SPSS Inc., Chicago, IL, USA) was used for statistical estimations. The statistical significance level was considered at p-value<0.05.

RESULTS

The age, BMI, and hormonal parameters including AMH and AFC of the three groups were represented in [Table/Fig-1]. Comparisons were made among different groups (OH group vs EU group, SCH group vs EU group, OH group vs SCH group) [Table/Fig-1]. Median age, BMI and total AFC were similar among the different groups and the differences between the median age, BMI and total AFC were not statistically significant (p-value>0.05). Serum TPOAb levels were high in OH group 366.1 IU/mL (IQR: 305.9-410) and SCH group 277.1 IU/mL (IQR: 222.3-320) when compared to EU group 6.05 IU/mL (IQR: 3.7-8.6). There were statistically significant differences (p-value<0.001) among the different groups (OH vs EU, SCH vs EU, OH vs SCH) [Table/Fig-1].

Serum TSH values were high in the OH group and SCH group, when compared to the EU group. Differences between serum TSH values among the three groups was a statistically significant (p-value <0.001). Serum fT4 values were low at 0.5 ng/dL (IQR;0.32-0.67) among Hashimoto's thyroiditis when compared to EU group 1.3 ng/dL (IQR;1.1-1.42) the differences between the serum fT4 values among OH vs EU, SCH vs EU, OH vs SCH groups was statistically significant, p-value<0.001. Serum FSH, LH, and E2 values were low in the OH group and SCH group when compared to the EU group. Differences between serum TSH values among the three groups was a statistically significant (p-value<0.05). Serum AMH values were low at 1.1 ng/mL (IQR: 0.27-1.3) in the OH group when compared to the EU group 1.45 ng/mL (IQR: 1.17-2.30), the difference was statistically significant (p-value <0.05). But the difference in AMH

Parameters	OH group Median (IQR)	SCH group Median (IQR)	EU group Median (IQR)	p-value (ANOVA)
Age (years)	37 (30.75-39.25)	35 (30.7-37.25)	37 (33.75-39)	[a]0.93, [b]0.28, [c]0.46
Body mass index (kg/m^2)	25.6 (25.07-26.07)	25.3 (23.5-26.0)	25.7 (25.17-26.0)	[a]0.9, [b]0.178, [c]0.07
TPOAb (IU/mL)	366.1 (305.9-410)	277.1(222.3-320)	6.05 (3.7-8.6)	**a<0.001, b<0.001, c<0.001**
TSH (μIU/mL)	16.45 (14.67-20.4)	7.2 (6.37-7.8)	2.5 (2.3-3.12)	**a<0.001, b<0.001, c<0.001**
fT4 (ng/dL)	0.5 (0.32-0.67)	1.1 (0.9-1.2)	1.3 (1.1-1.42)	**a<0.001, b<0.001, c<0.001**
FSH (mIU/mL)	4.3 (3.35-4.9)	5.25 (4.3-7.2)	10.4 (6.65-15.55)	**a<0.001,b0.002, c0.001**
LH (mIU/mL)	1.3 (1.17-2.15)	3.21 (2.81-6.22)	8.2 (4.8-9.25)	**a<0.001, b0.002, c<0.001**
Estradiol (pg/mL)	12.65 (11.67-15.12)	21.7 (19.02-23.67)	45.3 (27.42-60.82)	**a<0.001, b<0.001, c0.004**
AMH (ng/mL)	1.1 (0.27-1.3)	0.95 (0.3-1.57)	1.45 (1.17-2.30)	**a0.015,** [b]0.41, [c]0.27
Total AFC	12 (11-12.25)	12 (12.00-12.25)	12 (11.75-13.0)	[a]0.19, [b]0.48, [c]0.113

[Table/Fig-1]: Age, Body Mass Index, thyroid and ovarian reserve parameters among the different groups.
Bold p-values are significant; OH: Overt hypothyroidism; SCH: Subclinical hypothyroidism; EU: Euthyroid; HT: Hashimoto's thyroiditis; TPOAb: Antithyroid peroxidase antibodies; TSH: Thyroid stimulating hormone; fT4: free T4; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; AMH: Antimüllerian hormone; AFC: Antral follicle count. p-values: [a]OH group Vs. EU group, [b]SCH group Vs. EU group, [c]OH group Vs. SCH Group (ANOVA)

values among the SCH group vs EU group, OH group vs SCH group was not statistically significant [Table/Fig-1].

Correlation analysis of AMH with other parameters showed that the AMH values were negatively correlated with age among all the three groups, (OH group: r-value=-0.718; p-value <0.001, SCH group: r-value=-0.402; p-value=0.028, and EU group: r-value=-0.701; p-value <0.001). There was no significant correlation between the AMH values and BMI, TPOAb, fT4, FSH, LH, E2, and total AFC among all the three groups [Table/Fig-2]. Linear regression analysis was performed on total Hashimoto's cases (OH group+SCH group) to test the influence of independent variables on AMH levels (dependent variable). Linear regression analysis in total Hashimoto's Thyroiditis cases showed AMH levels were independently correlated with only age t-value=-3.03 and p-value=0.004 [Table/Fig-3].

Parameters	OH group		SCH group		EU group	
	r-value	p-value	r-value	p-value	r-value	p-value
Age (years)	-0.718	**<0.001***	-0.402	**0.028***	-0.701	**<0.001***
Body mass index (kg/m^2)	-0.167	0.378	-0.095	0.617	0.111	0.559
TPOAb (IU/mL)	-0.132	0.347	-0.040	0.835	0.219	0.246
TSH (µIU/mL)	-0.181	0.486	-0.275	0.247	0.177	0.348
fT4 (ng/dL)	0.241	0.199	0.189	0.316	-0.051	0.787
FSH (mIU/mL)	0.167	0.377	-0.226	0.230	-0.316	0.089
LH (mIU/mL)	0.028	0.883	-0.236	0.209	0.328	0.077
Estradiol (pg/mL)	-0.016	0.932	-0.175	0.356	-0.11	0.564
Total AFC	0.296	0.113	-0.86	0.653	0.242	0.197

[Table/Fig-2]: Correlation of serum AMH with other parameters in the OH group, SCH group and EU group.
Spearman correlation analysis r=correlation coefficient; *p-value <0.05 was considered as statistically significant

Parameters	Models				
	Unstandardised coefficients		Standardised coefficients		
	B	Standard error	Beta	t	p-value
Constant	4.48	2.97		1.508	0.138
Age (years)	-0.80	0.026	-0.420	-3.03	**0.004***
Body mass index (kg/m^2)	-0.011	0.090	-0.016	-0.122	0.903
TPOAb (IU/mL)	-0.004	0.002	-0.356	-1.78	0.081
TSH (µIU/mL)	0.039	0.032	0.334	1.20	0.236
fT4 (ng/dL)	0.605	0.604	0.248	1.00	0.322
FSH (mIU/mL)	0.037	0.064	-0.076	-0.569	0.572
LH (mIU/mL)	-0.067	0.056	-0.177	-1.19	0.237
Estradiol (pg/mL)	-0.022	0.023	-0.150	-0.992	0.326
Total AFC	0.059	-0.138	0.056	0.426	0.672

[Table/Fig-3]: Linear regression analysis of various independent variable against AMH (dependent variable) among total Hashimoto's cases (OH+SCH).
*Significant at p-value <0.05, Linear regression analysis was used
Unstandardised beta (B) represents the slope of the line between the predictor variable and the dependent variable

DISCUSSION

Thyroid autoimmunity is the most common autoimmune disorder in women of reproductive age, the effect of the autoimmune system on the female reproductive system was demonstrated by many studies [17-19]. It has been shown that autoantibodies were detected in women with premature ovarian failure, thyroid dysfunction or thyroid autoimmunity can affect the ovarian reserve [12]. Although underlying mechanisms of how thyroid antibodies affect ovarian reserve are not clearly understood, the possible mechanism may be that anti-TPO passes through follicle barrier during follicular evolution and that may result in the destruction and damaging of growing the follicles and oocytes. Thyroid antibodies seem to have a direct impact on ovarian tissue [20,21].

AMH has gained importance as a reliable marker of ovarian reserve. Several studies were conducted earlier to find out the association between ovarian reserve, AMH as a marker and thyroid autoantibodies, and TSH. A study by Polyzos NP et al., assessed the association between serum AMH levels, TSH, and thyroid autoantibodies levels and found that serum AMH levels were not associated with TPOAb or TSH levels [13]. Another study by Saglam F et al., showed lower serum AMH levels in patients with autoimmune thyroid disease than in controls [22]. However, in the multivariate analysis, they found that TSH was not the factor influencing AMH levels. Kuroda K et al., demonstrated that serum AMH levels showed an inverse correlation with serum TSH levels. But they did not include thyroid antibodies in their analysis [23].

In the present study, the authors have estimated the AMH, TSH, fT4, TPOAb, FSH, LH, E2, and AFC values among newly diagnosed Hashimoto's Thyroiditis patients with overt and subclinical hypothyroidism. The current study found that, serum AMH levels were low in the OH group, when compared to the EU group (controls). AMH values were negatively correlated with age among all the three groups. Age was found to be an independent risk factor affecting the AMH levels. There was no significant correlation between the AMH values and BMI, TPOAb, fT4, FSH, LH, E2, and total AFC among all the three groups. Present study results showed that, there was a negative correlation between age and AMH levels among all three groups. Age was found to be an independent risk factor affecting the AMH levels. There was no significant correlation between AMH values and TPOAb and TSH values in the present study, this was similar to a study conducted by ÖztürkÜnsal İ et al., [10].

Chen CW et al., [11] reported that positive TPOAb are associated with low ovarian reserve. The current study, found high TPOAb among Hashimoto's disease patients when compared to the euthyroid group but there was no significant correlation between AMH levels and TPOAb. Another study by Osuka S et al., [12] reported that TPOAb are not likely to affect ovarian reserve in euthyroid women with normal TSH, but elevated TSH was associated with decreased AMH levels. Studies by Polyzos NP et al., Korevar TIM et al., and Kucukler FK et al., reported that there was no relationship between thyroid hormone levels and AMH values [13-15]. The present study findings are similar to these studies. The current study could help to assess ovarian reserve among overt and subclinical Hashimoto's thyroid patients simultaneously and compared with the euthyroid subjects.

Limitation(s)

Newly diagnosed Hashimoto's thyroiditis patients were included in the present study; the effect of thyroid autoimmunity on ovarian reserve might have been inadequately assessed as authors did not measure thyroglobulin antibodies.

CONCLUSION(S)

The present study concluded that, there was significantly decreased ovarian reserve among overt hypothyroid individuals. Also there was no significant decrease of ovarian reserve among subclinical hypothyroid subjects. Age was found to be independent marker for decline in AMH levels irrespective of thyroid status. Thus, it was inferred that newly diagnosed Hashimoto's thyroiditis related overt hypothyroidism but not the subclinical hypothyroidism was associated with decreased ovarian reserve.

Acknowledgement

The authors would like to thank Dr Jyothi, Assistant Professor, Department of Obstetrics and Gynaecology for her help in the data collection and support throughout the study.

REFERENCES

[1] Krassas G, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702-55.
[2] Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol (Oxf). 2007;66(3):309-21. Doi: 10.1111/j.1365-2265.2007.02752.x. PMID: 17302862.
[3] Zhang SS, Carrillo AJ, Darling DS. Expression of multiple thyroid hormone receptor mRNAs in human oocytes, cumulus cells, and granulosa cells. Mol Hum Reprod. 1997;3(7):555-62.
[4] Persani L, Rossetti R, Cacciatore C, Bonomi M. Primary ovarian insufficiency: X chromosome defects and autoimmunity. J Autoimmune. 2009;33(1):35-41.
[5] Hsieh YT, Ho JYP. Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency-A nationwide Health Insurance Research Database study. Hum Reprod. 2021;36(6):1621-29. Doi: 10.1093/humrep/deab025. PMID: 33569594.
[6] Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al.Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol. 2007;23(5):279-83.
[7] Joshi JV, Bhandarkar SD, Chadha M, Balaiah D, Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. J Postgrad Med. 39(3):137-41.
[8] Vissenberg R, Manders VD, Mastenbroek S, Fliers E, Afink GB, Ris-Stalpers C, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. Hum Reprod Update. 2015;21(3):378-87.
[9] Tüten A, Hatipoğlu E, Öncül M, İmamoğlu M, Acikgöz AS, Yilmaz N, et al. Evaluation of ovarian reserve in Hashimoto's thyroiditis. Gynecological Endocrinology. 2014;30(10):708-11. Doi: 10.3109/09513590.2014.926324.
[10] Öztürkünsal İ, Hepşen S, Akhanlı P, Çalapkulu M, Sencar ME, Yalçındağ A, et al. Evaluation of serum anti-Müllerian hormone levels in women with Hashimoto thyroiditis in the reproductive age. Turk J Med Sci. 2021;51(2):716-21. Doi: 10.3906/sag-2012-177. PMID: 33705640; PMCID: PMC8203119.
[11] Chen CW, Huang YL, Tzeng CR, Huang RL, Chen CH. Idiopathic low ovarian reserve is associated with more frequent positive thyroid peroxidase antibodies. Thyroid. 2017;27(9):1194-1200. Doi: 10.1089/thy.2017.0139. PMID: 28810821.
[12] Osuka S, Iwase A, Goto M, Takikawa S, Nakamura T, Murase T, et al. Thyroid autoantibodies do not impair the ovarian reserve in euthyroid infertile women: A cross-sectional study. Horm Metab Res. 2018;50(7):537-42. Doi: 10.1055/a-0637-9430. Epub 2018 Jul 10. PMID: 29991084.
[13] Polyzos NP, Sakkas E, Vaiarelli A, Poppe K, Camus M, Tournaye H. Thyroid autoimmunity, hypothyroidism and ovarian reserve: A cross-sectional study of 5000 women based on age-specific AMH values. Hum Reprod. 2015;30(7):1690-96.
[14] Korevaar TIM, Mínguez-Alarcón L, Messerlian C, de Poortere RA, Williams PL, Broeren MA, et al. Association of thyroid function and autoimmunity with ovarian reserve in women seeking infertility care. Thyroid. 2018;28(10):1349-58.
[15] Kucukler FK, Gorkem U, Simsek Y, Kocabas R, Guler S. Evaluation of ovarian reserve in women with overt or subclinical hypothyroidism. Arch Med Sci AMS. 2018;14(3):521.
[16] Morales-Martínez FA, Sordia-Hernández LH, Ruiz MM, Garcia-Luna S, Valdés-Martínez OH, Vidal-Gutierez O. Association between thyroid autoimmunity and ovarian reserve in women with hypothyroidism. Thyroid Res. 2021;14(1):06. Doi: 10.1186/s13044-021-00095-0. PMID: 33752726; PMCID: PMC7983266.
[17] Hefler-Frischmuth K, Walch K, Huebl W, Baumuehlner K, Tempfer C, Hefler L, et al. Serologic markers of autoimmunity in women with polycystic ovary syndrome. Fertil Steril. 2010;93(7):2291-94.
[18] Fénichel P, Gobert B, Carré Y, Barbarino-Monnier P, Hiéronimus S, et al. Polycystic ovary syndrome in autoimmune disease. Lancet. 1999;353(9171):2210.
[19] Ott J, Aust S, Kurz C, Nouri K, Wirth S, Huber JC, et al. Elevated antithyroid peroxidase antibodies indicating Hashimoto's thyroiditis are associated with the treatment response in infertile women with polycystic ovary syndrome. Fertil Steril. 2010;94(7):2895-97.
[20] Monteleone P, Parrini D, Faviana P, Carletti E, Casarosa E, Uccelli A, et al. Female infertility related to thyroid autoimmunity: The ovarian follicle hypothesis. Am J ReprodImmunol. 2011;66(2):108-14.
[21] Serin AN, Birge Ö, Uysal A, Görar S, Tekeli F. Hashimoto's thyroiditis worsens ovaries in polycystic ovary syndrome patients compared to Anti-Müllerian hormone levels. BMC Endocr Disord. 2021;21(1):44. Doi: 10.1186/s12902-021-00706-9. PMID: 33750377; PMCID: PMC7941903.
[22] Saglam F, Onal ED, Ersoy R, Koca C, Ergin M, Erel O, et al. Anti-Müllerian hormone as a marker of premature ovarian aging in autoimmune thyroid disease. Gynecol Endocrinol. 2015;31(2):165-68. Doi: 10.3109/09513590.2014.973391. Epub 2014 Oct 16. PMID: 25319839.
[23] Kuroda K, Uchida T, Nagai S, Ozaki R, Yamaguchi T, Sato Y, et al. Elevated serum thyroid-stimulating hormone is associated with decreased anti-Mullerian hormone in infertile women of reproductive age. J Assist Reprod Genet. 2015;32(2):243-47.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Government Medical College Nalgonda, Telangana, India.
2. Associate Professor, Department of Biochemistry, ESIC Medical College and PGIMSR, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Veerendra Kumar Arumalla,
Associate Professor, Department of Biochemistry, ESIC Medical College and PGIMSR, KK Nagar, Chennai-600078, Tamil Nadu, India.
E-mail: drveerendraarumalla@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 16, 2022
- Manual Googling: Jul 18, 2022
- iThenticate Software: Aug 04, 2022 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 10, 2022**
Date of Peer Review: **Jul 16, 2022**
Date of Acceptance: **Aug 27, 2022**
Date of Publishing: **Oct 01, 2022**