

## Ovarian Reserve in Euthyroid Hashimotos Thyroiditis in Women of Reproductive Age

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### Abstract:

**Background:** Hashimotos thyroiditis is the most common organ specific autoimmune disorder in the women of reproductive age group. Ovary is the most common organ effected in any autoimmune disorder. Hashimotos thyroiditis is associated with diminished ovarian reserve and ultimately result in primary ovarian insufficiency. The aim of the present study is to assess the ovarian reserve in euthyroid hashimoto's thyroiditis and compare with thyroid peroxidase (TPO) antibody negative controls and to evaluate the association of serum anti mullerian hormone (AMH) with TPO antibody titres in hashimoto's thyroiditis.

**Materials and Methods:** We included 40 patients in our study with age group between 25-40 years. The cases were 20 women with hashimotos thyroiditis group who were euthyroid with or without treatment. The controls were 20 women with TPO antibodies negative status. We measured, anti TPO antibodies and antimullerian hormone levels (AMH) and antral follicle count (AFC) for assessment of ovarian reserve in our study. Ovarian reserve is considered decreased if serum AMH value less than 1.05 ng/ml. Low antral follicular count is considered to be less than 6 antral follicles.

**Conclusion:** Finally ovarian reserve was similar between euthyroid hashimoto's thyroiditis and healthy controls suggesting that thyroid autoimmunity has no influence on ovarian reserve. Age, body mass index and serum thyroid stimulating hormone did not influence the serum AMH levels.

**Key Word:** hashimotos thyroiditis, ovarian reserve, antimullerian hormone, antral follicle count, thyroid peroxidase antibodies.

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### I. Introduction

Hashimoto's thyroiditis is the most common organ-specific autoimmune disorder affecting approximately 18% of population.<sup>1</sup> It may often remain undiagnosed as it may present without overt thyroid dysfunction.<sup>2</sup> Thyroid dysfunction has been linked to reduced fertility. Majority of data suggest that ovarian function is disturbed and frequency of miscarriages and infertility are increased in patients with autoimmune thyroid disease (AITD). Ovary is commonly the target of an autoimmune attack in cases of organ or non-organ-specific autoimmune disorders, leading to the ovarian dysfunction which can eventually end up in primary ovarian insufficiency (POI) in its most extreme clinical presentation. Among autoimmune disorders, thyroid disorders are most commonly associated with ovarian insufficiency and found in 27 % of women with POI.<sup>3</sup> Several studies showed a strong correlation between thyroid antibodies and specific causes of infertility as endometriosis, polycystic ovarian syndrome (PCOS) and diminished ovarian reserve. Patients with thyroid peroxidase antibodies (TPO Ab), even in the presence of euthyroidism, are known to have an increased risk for miscarriage.<sup>4</sup> The researchers hypothesized that the presence of antithyroid antibodies may cause antibody-mediated cytotoxicity in the growing ovarian follicle and damage to the maturing oocyte, which may reduce its

quality and its developmental potential.<sup>5</sup> Belvisi et al reported that 40% of 45 women with POI were positive for at least one organ-specific auto-antibody, the most common being anti-thyroid antibodies (20%).<sup>6</sup> In addition, a recent study investigated the presence of TPO Abs in a large cohort of POI and found it in 24% of these cases.<sup>7</sup> In this context, hashimotos thyroiditis is likely to be associated with ovarian dysfunction and diminished ovarian reserve. Ovarian reserve plays a crucial role in achieving pregnancy and menstrual regularity in reproductive age women. Many parameters have been introduced and utilized in clinical practice so far but anti mullerian hormone (AMH) and antral follicle count (AFC) appear to be the most useful markers of ovarian reserve in addition to chronological age. Serum AMH levels are also shown to decrease before follicular stimulating hormone (FSH) rises in normally cycling women.<sup>8</sup> Diminished ovarian reserve describes women of reproductive age having regular menses but whose response to ovarian stimulation is reduced compared with women of comparable age.<sup>9</sup> Women with diminished ovarian reserve represent approximately 24% of the infertile population and their treatment remains a challenge for clinicians. This study was designed to evaluate the possible association between this significantly prevalent hashimoto's thyroiditis and ovarian reserve. The aim of the present study is to assess the ovarian reserve in euthyroid hashimoto's thyroiditis and compare with TPO antibody negative controls and to evaluate the association of serum anti mullerian hormone (AMH) with TPO antibody titres in hashimoto's thyroiditis.

## **II. Material And Methods**

This is a cross sectional study. The present study was conducted in the department of endocrinology, Andhra medical college, King George Hospital, Visakhapatnam, Andhra Pradesh. Patients were enrolled who presented to the outpatient department in the Department of Endocrinology at King George Hospital. The duration of the study is one year between january 2019 to december 2019.

### **Inclusion criteria:**

1. Females in age group 25-40 years , euthyroid Status, ultrasound neck suggestive of hashimotos thyroiditis, positive TPO antibodies were included in the study.

### **Exclusion criteria:**

1. Use of oral contraceptives, gonadotropin releasing hormone agonists (GnRH) agonists, exposure to chemotherapy or radiotherapy, subjects with any chronic systemic illness, ovariectomy patients, polycystic appearance on imaging, overweight and obese patients.  
2. Age and body mass index (BMI) matched women without comorbid illness, normal thyroid function, negative for TPO antibodies were included in the control group.

### **Procedure methodology**

Diagnosis of hashimotos thyroiditis was determined by the presence of elevated TPO antibodies levels and heterogeneity of thyroid gland on ultrasound neck. Thyroid ultrasound was performed using a Toshiba Xario 2 device with a 7-11 MHz probe. The thyroid was considered hypo echogenic when its signal was equal or below the echogenicity of the surrounding neck muscles. Venous blood samples from each study participant were obtained to determine free tetraiodothyronine (FT4) , thyroid stimulating hormone (TSH) and TPO antibodies. TSH, FT4 and TPO were assayed using chemiluminescence method (Rosche, ELECSYS 2010, Hitachi high technology corporation, Tokyo, Japan).

The normal ranges for TSH, FT4 and TPO antibodies were 0.5-4.5  $\mu$ IU/ml, 0.9-1.7 ng/ml and  $\leq$ 34 IU/L respectively. TPO antibodies was considered positive if the titre was more than 34 IU/ml. Venous blood samples were collected for all participants on the 3rd or 4th day of follicular phase of menstrual cycle in the morning between 8- 10 AM and measured for AMH. AMH concentrations were measured by Chemiluminescence immunoassay. Ovarian reserve is considered decreased if serum AMH value less than 1.05 ng/ml.

On the same morning, Transvaginal ultrasonographic evaluation was performed with 5-7.5 MHz transducer. The operator who was unaware of all patient information counted the total numbers of ovarian follicles measuring between 2-10 mm in both ovaries. Low antral follicular count is considered to be less than 6 antral follicles.

### **Statistical analysis**

For statistical analysis SPSS Version 17 software was used, the data was presented as mean  $\pm$  standard deviation. Independent sample t test was used for comparison of means to calculate significance. The P value  $\leq$ 0.05 was considered statistically significant

### III. Result

A total of 40 subjects, out of which 20 women with hashimotos thyroiditis were regarded as cases and 20 women with age and body mass index (BMI) matched thyroid peroxidase (TPO) antibody negative women were regarded as controls.

The baseline characteristics of cases and controls were shown in table 1. All of the subjects presented with goiter. Most of them had non-specific symptoms. Subjects with hashimotos thyroiditis and controls had regular menstrual cycles. All are married with history of primary infertility in one case. History of spontaneous miscarriage present in one case. Two women are nulliparous. Among 20 women with hashimotos thyroiditis eight were on replacement therapy with levothyroxine.

Parameter	Cases (n= 20)	Controls (n=20)
Age in yrs ( Mean ± SD)	32.70 ± 4.16	32.55 ± 3.94
BMI in Kg/m <sup>2</sup> ( Mean ± SD)	21.12 ± 0.99	21.47 ± 0.80
Age at Menarche in yrs ( Mean ± SD)	13.5 ± 0.9	13.3 ± 1.2
Menstrual cycle length in days ( Mean ± SD)	27.5 ± 5.8	29.2 ± 7.2
Pregnancies ( Mean ± SD)	2 ± 1.2	2 ± 1.5
Number of live births (Mean ± SD)	1.8 ± 1.2	1.9 ± 1
Family H/o thyroid dysfunction(n)	5	3

Table 1. The Baseline Characteristics of Cases and Controls

Thyroid function tests and TPO antibodies were represented in table 2. There was no significant difference between cases and controls in terms of levels of free T4 and TSH between the two groups. however there was significant difference in terms of TPO antibodies between cases and controls with a p value of 0.001.

Parameter	Cases	Controls	P Value
FREE T4 ( ng/dl)	1.18 ± 0.23	1.18 ± 0.20	0.933
TSH ( µIU/ml)	2.84 ± 1.00	2.40 ± 1.19	0.211
TPO Abs ( IU/ml)	423.28 ± 344.73	7.77 ± 4.96	<b>0.001</b>

Table 2. Thyroid Function Tests and TPO Antibodies in Cases and Controls

Mean AMH levels and AFC were represented as shown in table 3. Total antral follicle count(AFC) was similar in the two groups with no significant difference. Similarly there was no significant difference between cases and controls regarding AMH levels.

Parameter	Cases	Controls	P Value
AMH (Mean ±SD)	1.42 ± 0.88	1.32 ± 0.64	0.704
AFC (Mean ±SD)	7.05 ± 3.96	7.15 ± 2.99	0.929

Table 3. Mean AMH & AFC in Cases and Controls

Mean AMH levels according to TPO antibody titers were represented as shown in table 4. The cases were categorized into three groups according to TPO antibody titres. 20% of cases had TPO antibody titers between 35-100 IU/L, 50 % of cases had TPO Ab titers between 101-600 IU/L and 30% had TPO Ab titers >600 IU/L. There were decreasing levels of AMH with increasing levels of TPO antibody titers. This could be due to dose dependent effect of antibodies on granulosa cells of ovary or number of ovarian follicle.

TPO Ab Titers	Number of Patients	Mean AMH	Standard Deviation
35 -100 IU/L	4	2.25	1.58
101 -600IU/L	10	1.41	0.42
>600 IU/L	6	0.87	0.46

Table 4. Comparison of AMH across TPO Ab titers in Cases

5.Results for serum AMH levels across age groups in cases and controls were represented in table 5. The levels of AMH means were decreasing as the age increases with no significant difference found between three groups (P= 0.118).

Age ranges	N	Mean AMH	SD
25-30 yrs	6	1.98	1.21
31-35 yrs	10	1.05	0.54
36-40 yrs	4	1.50	0.70

Table 5. Comparison of AMH Across Age Ranges in Cases

The levels of AMH in the control group were showed in table 6. serum AMH levels were decreasing with increasing age with no significant difference found between three groups (P= 0.659).

Age Ranges	N	Mean AMH	SD
25-30 yrs	6	1.52	0.45
31-35 yrs	10	1.27	0.69
36-40 yrs	4	1.16	0.82

Table 6. Comparison of AMH Across Age Ranges in Controls

Results for serum AMH levels across the euthyroid range with low TSH levels ( $\leq 2.5$   $\mu\text{IU/ml}$ ) and high TSH ( $> 2.5$   $\mu\text{IU/ml}$ ) in hashimotos thyroiditis cases and controls. In hashimotos thyroiditis group 7 cases (35%) had TSH  $\leq 2.5$   $\mu\text{IU/ml}$  and 13 cases (65%) had TSH  $> 2.5$   $\mu\text{IU/ml}$ . Mean AMH in TSH  $\leq 2.5$   $\mu\text{IU/ml}$  group was 1.29 ng/ml and mean AMH in TSH  $> 2.5$   $\mu\text{IU/ml}$  group was 1.48 ng/ml with no significant difference between two groups ( $P > 0.05$ ). In the control group, ten individuals (50%) had TSH  $\leq 2.5$   $\mu\text{IU/ml}$  and ten individuals (50%) had TSH  $> 2.5$   $\mu\text{IU/ml}$ . Mean AMH in TSH  $\leq 2.5$   $\mu\text{IU/ml}$  group was 1.50 ng/ml and mean AMH in TSH  $> 2.5$   $\mu\text{IU/ml}$  group was 1.14 ng/ml with no significant difference between two groups ( $P > 0.05$ ).

#### IV. Discussion

Ovarian reserve plays crucial role in menstrual regularities and in achieving pregnancy in women of reproductive age group. The various hormonal markers and ultrasound parameters are used for evaluation of ovarian reserve in women. These include age, follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), inhibin B, antimullerian hormone (AMH), ovarian volume, ovarian antral follicle count (AFC), and ovarian biopsy. Among all these, estimation of AMH levels and AFC are most useful markers for evaluation of ovarian reserve. Ovary is a common target of autoimmune attack in organ specific and non organ specific autoimmune disorders which leads to ovarian dysfunction and ultimately end up in premature ovarian insufficiency. Autoimmune thyroid disorders are the most prevalent causes of premature ovarian insufficiency among all autoimmune disorders.<sup>10,11</sup>

Women of reproductive age group between 25-40 years were only included in the present study as AMH levels are low during prepubertal development, rise during early puberty and reach a plateau at 20-25 years of age, followed by a gradual decline thereafter until becoming undetectable around menopause. Hence, it appears that AMH can only be used to assess the extent of ovarian aging in women beyond 25 years of age. In the present study, there was no significant correlation found between the age and AMH even though the levels were decreasing with advancing age. This was similar to study done by Fatma saglam et al<sup>12</sup> who also recruited women younger than 40 yrs of age where as study done by Abdullah tuten et al<sup>13</sup> there was significant negative correlation between age and AMH. Negative correlation of age with AMH in that study might be due to inclusion of more number of elderly women as with increasing age there would be decline in ovarian follicle pool and quality of oocytes within and thereby reproductive potential of women. In the present study 80% of women were below 35 years age, therefore no significant effect on AMH was observed. In the present study age has no influence on ovarian reserve as most of the included women were between 25-40 years of age.

In a study done by Ozgur pirgon et al<sup>14</sup> mean AMH in hashimotos thyroiditis group was 10.6 ng/ml and in the control group was 7.5 ng/ml with significant difference found between two study groups ( $P = 0.007$ ). In study done by Abdullah tuten et al mean AMH was 4.82 ng/ml in hashimotos thyroiditis group and in the control group was 2.44 ng/ml with significant difference between two groups ( $P = 0.025$ ). Both O.pirgon et al and Abdullah tuten et al studies suggested an association of autoimmune thyroid disease with polycystic ovarian disease. In study done by Ozgur pirgon et al<sup>14</sup> serum AMH concentrations were significantly correlated positively with age. Those results were consistent with study done by S. Lie Fong et al<sup>15</sup> which showed that before the age of 15.8 yr, serum AMH and age were positively correlated. Thereafter AMH levels remained stable, and consequently, the correlation between AMH and age did not reach statistical significance. From the age of 25 years there was an inverse correlation between AMH and age.

In a study done by Fatma saglam et al mean AMH in hashimotos thyroiditis group was 1.16 ng/ml and in the control group was 1.28 ng/ml with significantly lower values in hashimotos thyroiditis group ( $P = 0.001$ ). The lower levels of AMH in hashimotos thyroiditis cases might be due to influence of antibodies either on ovarian granulosa cells diminishing the secretion of AMH or due to influence on ovarian follicles depleting the follicle pool or both. Autoimmune mechanisms considered to be a cause of primary ovarian failure in about 20-30% of cases. Thyroid autoimmune disease, most commonly Hashimoto's thyroiditis, is present in 14 to 27% of women at initial diagnosis of primary ovarian insufficiency. The evidence for an autoimmune etiology is threefold. The presence of lymphocytic oophoritis, autoantibodies to ovarian antigens, and associated autoimmune disorders.

In the present study, mean AFC in hashimotos thyroiditis group was 7.05 vs in control group was 7.15 with no significant difference found between cases and controls ( $P = 0.92$ ). In a study done by O.pirgon et al mean AFC in hashimotos thyroiditis group was 11 and in the control group was 13.4 with no significant difference found between two study groups with ( $P = 0.176$ ). In a study done by Abdullah tuten et al mean AFC

in hashimotos thyroiditis group was 6.84 and in the control group it was 6.08 with no significant difference between two groups ( $P = 0.297$ ). The present study results were similar to the previous studies in terms of AFC.

Mean body mass index(BMI) in the present study in the cases was  $21.12 \text{ kg/m}^2$  and in control group was  $21.47 \text{ kg/m}^2$  with no significant difference between two groups ( $P = 0.23$ ). In the present study women who were overweight and obese were excluded as it might be confounding factor because BMI negatively correlates with AMH. In a study done by Ellen W. Freeman et al<sup>16</sup> Obese women have lower AMH levels compared to non-obese women in the late reproductive years. AMH levels were 65% lower in obese women compared to non-obese women (0.016 ng/ml and 0.046 ng/ml, respectively with  $P = 0.03$ ).

In a cross sectional study by Nikolaos p. polyzos et al,<sup>17</sup> which evaluated association between thyroid autoimmunity, hypothyroidism and diminished ovarian reserve , 4894 women were categorized according to the AMH levels in to three groups : 3929 women with normal ovarian reserve, 487 women with low ovarian reserve and 478 women with high ovarian reserve. The mean serum FT4 levels (1.2 ng/dl) were same in all groups with low,normal and high ovarian reserve with no significant difference (  $P = 0.611$ ). Similarly, TSH levels did not demonstrate any difference in women with low (1.6 mIU/l), normal (1.5 mIU/l) and high ovarian reserve (1.5 mIU/l). No differences were observed between groups in the prevalence of overt or subclinical hypothyroidism (4.1% in low, 4.6% in normal and 3.8% in high ovarian reserve women,  $P = 0.645$ ). The results of the study suggest no effect of thyroid disorders on ovarian reserve.

In a study done by Ferit kerim kukuckler et al<sup>18</sup> which included women with newly diagnosed autoimmune thyroid disorder aged between 20-40 yrs in three groups , subclinical hypothyroidism( $n = 21$ ), overt hypothyroidism ( $n = 21$ ) and controls ( $n = 32$ ) . No significant difference was found among all three groups in regard to ovarian reserves measured by AMH values ( $P = 0.19$ ) and AFC ( $P = 0.80$ ). In a study done by Keiji Kuroda et al<sup>19</sup> elevated serum TSH is associated with decreased AMH in infertile women of reproductive age ( $P = 0.036$ ). Therefore, TSH may be a factor influencing ovarian reserve in infertile patients. Given that subclinical hypothyroid women are at an increased risk of infertility, elevated TSH levels may have deleterious effects on ovarian function. Michalakakis et al.<sup>20</sup> also reported clinical data in high prevalence of diminished ovarian reserve in the infertile patients with elevated serum TSH levels. Thyroid hormone plays an important role in follicular development. In addition, TSH directly suppressed follicle development in a concentration-dependent manner. However, TSH levels in infertile patients in Keiji Kuroda et al study were almost within the normal range; therefore, ovarian function of infertile patients is somehow more susceptible to TSH compared with that of healthy fertile women. In a study done by Andrea Weghofer et al<sup>21</sup> which was done in 225 infertile women with normal thyroid function (TSH, 0.4-4.5  $\mu\text{U/mL}$ ), even after adjustment for thyroid autoimmunity and age, TSH  $< 3 \mu\text{U/m L}$  in euthyroid infertile patients is associated with significantly higher AMH levels than patients with TSH  $> 3 \mu\text{U/m L}$ . This observation suggest a direct beneficial effect of lower TSH levels on follicular recruitment. However in our study, we included all euthyroid patients both in cases as well as controls and we did not found any significant difference between TSH levels and AMH levels when we divided into those with TSH less than 2.5  $\mu\text{U/ml}$  and more than 2.5  $\mu\text{U/ml}$ . Mean AMH was 1.29 ng/ml and 1.48 ng/ml respectively with no significant difference between two groups ( $P>0.05$ ) in cases and similar results were found in the control group also.

In a study done by Nikolaos P. Polyzos et al in 4894 women, no significant differences were observed in the prevalence of TPO antibodies among women with low (12.1%), normal (10.3%) and high (9.8%) ovarian reserve ( $P = 0.423$ ) suggesting no influence of thyroid autoimmunity on ovarian reserve. In a study done by Andrea Weghofer et al,<sup>22</sup> which evaluated the relationship between TSH levels and embryo quality in euthyroid women with diminished ovarian reserve undergoing in vitro fertilization ,TPO Abs significantly affected embryo quality in women with low-normal TSH levels ( $P = 0.045$ ). In women with high-normal TSH levels, increasing TSH had a negative impact on embryo quality ( $P = 0.027$ ). A trend towards impaired embryo quality with TPO antibodies was also observed in these patients ( $P= 0.057$ ). Positive correlation between AMH and anti ovarian antibodies was in consistent with Shamilova et al<sup>23</sup> study which showed that women with autoimmune driven premature ovarian failure had significantly higher AMH levels in comparison to non-autoimmune driven premature ovarian insufficiency.

The main limitation of the present study was small sample size. Though AMH significantly declined with increasing TPO Ab titers in cases the difference is not significant between cases and controls. If large sample was taken,the effect of TPO antibodies might be better evident. Other limitations were that the hashimotos thyroiditis group included both euthyroid women who were treatment naive and patients who were euthyroid on replacement with thyroxine, so the influence of previous hypothyroidism on ovarian reserve might be a confounding factor. The duration of autoimmunity was not known in this cross sectional study. Longer duration of autoimmunity might have an effect on ovarian reserve.

## V. Conclusion

Ovarian reserve was similar between euthyroid Hashimoto's thyroiditis and healthy controls suggesting that thyroid autoimmunity has no influence on ovarian reserve. A significant decline of AMH with increasing TPO Ab titers was observed though there was no correlation of serum AMH with TPO antibodies. Serum AMH significantly correlated with antral follicle count in both cases and controls supporting its role as sensitive marker of ovarian reserve.

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