



ORIGINAL ARTICLE

## Comparison of thyroid hormone profile (T3, T4, TSH, ANTI TPOAB, & TBG) among fertile and infertile females.

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**ABSTRACT... Objective:** To compare thyroid hormone profile (T3, T4, TSH, Anti TPOAb, & TBG) among fertile and infertile females. **Study Design:** Case-control study. **Setting:** Department of Physiology and Department of Gynecology and Obstetrics, JPMC Karachi, BMSI. **Period:** Jan 2018 to Jan 2019. **Material & Methods:** There were 88 participants in the sample, who were split into two groups. Infertile group (group A) and control group (group B). Non-probability purposive sampling was employed because each group's subjects were chosen based on specified standards. In the current investigation, all subjects who met the eligibility requirements were registered. Each subject who took part gave their written consent. Information obtained was held in strict confidence. Data was analyzed using IBM SPSS version 23. **Results:** Serum T3, T4, TSH, anti TPOAb, and TBG levels differed significantly between the two study groups. There was significant mean difference obtained for TSH and anti TPO antibodies between fertile and infertile samples with p-value less than 0.05. **Conclusion:** In this study, all the subjects had T3, T4, TSH & TBG levels within the normal pre-pregnancy reference range. A trend towards subclinical hypothyroidism and the incidence of anti-thyroid antibodies was observed within females who had UE infertility, when their thyroid hormone profile was compared with fertile females.

**Key words:** Antibodies, Infertility, Thyroid, Hypothyroidism.

### INTRODUCTION

Infertility can be described classically as the inability to conceive after a year of frequent intercourse and not using contraception. However, data show that the recorded incidence of infertility in Pakistan is around 22 percent, with the primary accounting for 3.5 percent and the secondary accounting for 18.4 percent.<sup>1,2</sup>

Unexplained infertility (UI) refers to lack of detection of a definite cause for inability of a couple to achieve pregnancy after attempting conception for 12 months despite undergoing a thorough evaluation. The elements that explain the major factors of female infertility include ovulatory dysfunction, damage of fallopian tubes and endometriosis.<sup>3</sup> The thyroid gland regulates metabolic rate, which is then processed throughout the body by producing two hormones known as triiodothyronine and thyroxine (T4).

Both of these hormones play a significant role in the process of growth and development, — in particular in the brain development process.<sup>4</sup>

Thyroid disorders are commonly referred to as hyperthyroidism and hypothyroidism. Furthermore, a subclass of euthyroid patients who have positive thyroid autoantibodies has been discovered.<sup>5</sup> It is worth noting that the role of these antibodies in reproductive health has received greater attention in recent years.<sup>6</sup>

Furthermore, hypothyroidism in childhood and adolescence is linked to delayed sexual maturation. As a result, adulthood is characterized by menstrual problems and ovulation disruption.<sup>7</sup> Provided that thyroid hormone chooses to play an active role in embryonic development, thyroid disease had also long been linked to a rise in the risk of miscarriage.<sup>8</sup>

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Hyperthyroidism, a thyroid disorder, could have a significant impact on pregnancy.<sup>9</sup> The most severe repercussions include preterm delivery, preeclampsia, restricted growth, heart failure, and fetal death.<sup>10</sup> In Pakistan, the occurrence of hyperthyroidism and subclinical hyperthyroidism is 5.1% and 5.8%, respectively. Likewise, hypothyroidism and subclinical hypothyroidism were observed in 4.1% and 5.4% of the population, respectively.<sup>1</sup>

According to the growing evidence from experimental and clinical studies it states that hypothalamic-pituitary-ovarian axis as well as the hypothalamic-pituitary-thyroid axis have a physiological relationship.<sup>11,12</sup> According to American thyroid association guidelines, 2017, the Thyroid Profile Normal Ranges are, TSH (0.39 -6.16 mIU/L), T3 (52-185 ng/dl), T4 (4.4-10.8 µgm/dl), TBG (11-27 mg/Litre) and Anti TPO (>35 U/ml).

Thyroid dysfunction has been implicated in the spectrum of female infertility, as per studies.<sup>13</sup> Untreated and undetected thyroid disease may play a role in infertility; thus, awareness of thyroid condition in infertile couples is critical, because of its significant, recurring, and frequently preventable or reversible effect on infertility.<sup>14</sup>

A review of the available literature reveals that although there are numerous foreign studies on the subject, not really enough research has been carried out at the local level. The current study is proposed with the rationale of evaluating the association of thyroid dysfunction as well as thyroid autoimmunity with unexplained infertility, which will assist in the creation of appropriate interventions to reduce the incidence of infertility caused by undiagnosed or untreated thyroid dysfunction.

## **MATERIAL & METHODS**

This case control study was carried out in department of Physiology, BMSI, JPMC Karachi in collaboration with department of Gynaecology and Obstetrics JPMC. Duration of study was 1 year from Jan 2018 till Jan 2019.

The sample size is calculated using online available software open epi.com ([http://openepi.com/menu/oe\\_menu.htm](http://openepi.com/menu/oe_menu.htm)) with 95% confidence interval, 80% power of the test 5% of margins of error, sample size was calculated as 88 with distribution of 44 in each of two groups.

The two groups comprised of: Group A: Women with Unexplained Infertility (Cases) Group B: Healthy Parous Women (Controls).

Non-probability purposive sampling was used as the subjects were selected in each group according to predetermined criteria. Inclusion criteria for group A (Cases) was women at reproductive age(20-45 yrs) and UE infertile women having >12 months of infertility, 25-35 days of regular menstrual cycles, Endocrinological proof of ovulation, having a Standard hysterosalpingogram, normal semen analysis of their partner. While for controls it was healthy, parous women.

The exclusion criteria was women with diagnosed infertility of their partner, with menstrual irregularities & an-ovulatory cycles, more than 45 years of age, metabolic disorder like Diabetes, Obesity, Hypertension, taking Oral Contraceptive Pills, with intrauterine device placement and gynecological problems like polyps, malignancy, cyst, fibroid and hyperplasia.

After getting the approval of synopsis and the permission for data collection the data was collected. All the subjects fulfilling the selection criteria were registered in the present study. A written consent was obtained from each participating subject. All the relevant information was taken on a questionnaire designed for the present study (appendix 3). It included patient`s demographics (name, age), duration of marriage, height (cm), weight (kg), BMI (kg/m<sup>2</sup>), past medical /surgical/gynecological history, serum T3, T4, TSH, TBG & anti TPO antibodies levels. Further, data was entered by independent observers who were not the part of study which minimized the risk. Data was stored and analyzed using IBM SPSS version 23.0, mean and standard

deviation were reported for age, age at marriage, marriage duration and body mass index, count and percentages were reported for education, family system, and menstrual cycle information, mean comparison of Thyroid profile and antiTPO antibodies was done between fertile and infertile samples using independent sample t-test.

## RESULTS

Significant differences in the levels of serum T3, T4, TSH, anti TPOAb and TBG were seen among both the study groups.

The comparison of thyroid profile and antiTPO antibodies between study groups in table-I shows that among infertile samples, mean T3 was  $131.6 \pm 24.04$  ng/dl, mean T4 was  $9.37 \pm 1.44$   $\mu$ gram/dl, mean TSH was  $2.47 \pm 1.97$  mIU/L, mean TBG was  $21.699 \pm 4.61$  mg/L and mean antiTPO was  $36.08 \pm 10.60$  IU/ml, whereas among fertile samples, mean T3 was  $135.57 \pm 32.55$  ng/dl, mean T4 was  $10.10 \pm 2.51$   $\mu$ gram/dl, mean TSH was  $1.10 \pm 2.14$  mIU/L, mean TBG was  $22.747 \pm 7.486$  mg/L, and mean antiTPO was  $20.13 \pm 12.30$  IU/ml. So there was significant mean difference obtained for TSH and antiTPO

antibodies between fertile and infertile samples with p-value less than 0.05.

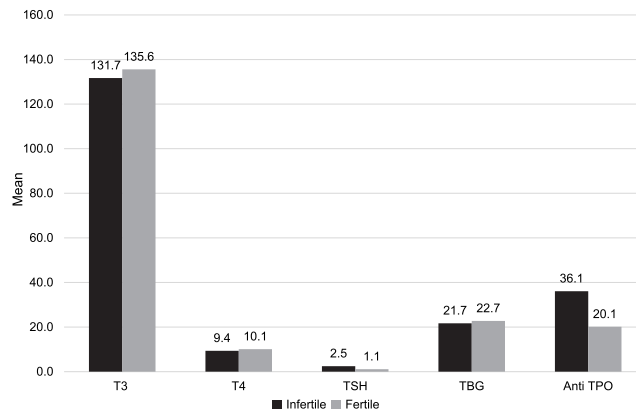


Figure-1. Comparison of thyroid profile and antiTPO Antibodies

## DISCUSSION

The purpose of our study was to evaluate the association of thyroid dysfunction and thyroid autoimmunity with unexplained infertility, which in turn helps to design appropriate interventions that will decrease incidence of infertility caused by undiagnosed or untreated thyroid dysfunction.

	Infertile	Non Infertile	P-Value
Age (years)	$31.57 \pm 6.12$	$32.33 \pm 5.83$	0.556
Age of marriage (years)	$23.32 \pm 4.84$	$20.13 \pm 6.32$	0.025*
Duration of Marriage (years)	$8.25 \pm 4.43$	$10.35 \pm 6.81$	0.097
BMI kg/m <sup>2</sup>	$28.53 \pm 4.38$	$23.41 \pm 1.67$	<0.001*

Group A: Women with unexplained infertility (cases)

Group B: Healthy parous women (controls)

Mean  $\pm$  SD is given in table

\*p<0.05 was considered significant using independent sample t-test

Table-I. Baseline characteristics of study groups

	Infertile	Fertile	P-Value
T3 (ng/dl)	$131.67 \pm 24.04$	$135.52 \pm 32.55$	0.525
T4 ( $\mu$ g/dl)	$9.36 \pm 1.43$	$10.09 \pm 2.51$	0.097
TSH (mIU/L)	$2.47 \pm 1.97$	$1.12 \pm 2.14$	0.003*
TBG (mg/Litre)	$21.69 \pm 4.62$	$22.74 \pm 7.48$	0.431
antiTPO (IU/ml)	$36.08 \pm 10.62$	$20.13 \pm 12.31$	<0.001*

Group A: women with unexplained infertility (cases)

Group B: healthy parous women (controls)

Mean  $\pm$  SD is given in table

\*p<0.05 was considered significant using independent sample t-test

Table-II. Thyroid profile and antiTPO levels of study groups

Age distribution of the women of both the groups varied between 20-35 years. When we studied the descriptive analysis of the group A and group B, we found that infertile sample had mean age  $31.57 \pm 6.12$ , whereas fertile samples had mean age  $32 \pm 6.15$  with p value ( $>0.05$ ) showing no significant difference between both the groups.

BMI of group A was  $28.53 \pm 4.38$  and group B was  $23.41 \pm 1.67$  (p value  $<0.001$ ). This shows that women with UI have BMI greater than the fertile women. The increase in BMI contributes to insulin resistance which is a contributing factor of infertility. Our work is similar to the published work of Chitme et al.<sup>15</sup>

The mean of TSH was  $2.47 \pm 1.97$  mIU/L in women with UI, as compared to  $1.10 \pm 2.14$  mIU/L TSH levels in controls which suggested that mild abnormalities in thyroid function may contribute to some cases of UI. Thus, it is important to go for complete thyroid evaluation in all the patients with UI. It also raises the question of whether thyroid hormone replacement in women with TSH levels  $\geq 2.5$  mIU/L may be an economical first step in treating UI. Although, in current practices, guidelines do not recommend treating women with a TSH  $\geq 2.5$  mIU/L who are attempting to conceive naturally, however, some practitioners use this lower cutoff to initiate treatment.<sup>16,17</sup>

In current study, mean T3 levels was  $131.6 \pm 24.04$  ng/dl in cases as compared to  $135.57 \pm 32.55$  ng/dl in controls, showing no significant difference. Although the T3 levels in infertile samples are decreased as compared to controls but important point is that the levels are within the normal, pre-pregnancy reference range.

In present study mean tetraiodothyronine (T4) levels was  $9.37 \pm 1.44$   $\mu$ gram/dl in infertile samples as compared to  $10.10 \pm 2.51$   $\mu$ gram/dl in controls, showing no significant difference. Although, the T4 levels are comparatively low in infertile samples however, the levels are within the normal, pre-pregnancy reference range. A large number of traditional investigators and bioassays of hormones have been practiced in the diagnosis and management of infertility for a long time.

By extensive studies it has been proved that for normal sexual function, thyroid secretion of T3 and T4 needs to be approximately normal (if not fully normal).<sup>18</sup>

In present study mean TSH levels in infertile samples were  $2.47 \pm 1.97$  mIU/L as compared to  $1.10 \pm 2.14$  mIU/L in controls, difference was significant.

Another study found that the women who were thyroid antibodies positive had a significantly higher TSH and lower free thyroxin T4 compared with the control group. Sieiro Netto, (2004) found that risk of miscarriage was significantly higher in TPO-Ab positive women and in women with high TSH levels.<sup>19</sup>

Interestingly, in our study we found a significant increase in anti TPO-Ab titers in infertile patients. Mean anti TPO-Ab levels in infertile samples were  $36.08 \pm 10.60$  IU/ml as compared to  $20.13 \pm 12.30$  IU/ml in controls, showing highly significant difference ( $<0.05$ ). In the most studies for determining the relationship between autoantibodies and infertility, TPO-Ab have been measured, in addition to TSH, T3 and T4 levels.<sup>20</sup> Our results are in agreement with other researchers who found a relationship between thyroid autoantibodies, and infertility.

Thyroid dysfunction, including both hypothyroidism and hyperthyroidism can lead to infertility, abortions, still births, failure of lactation, menorrhagia and menstrual abnormalities.<sup>21,22</sup> The results of our study show that although all the subjects had T3, T4, TSH & TBG levels within the normal pre-pregnancy reference range but a trend towards subclinical hypothyroidism and the incidence of anti-thyroid antibodies was observed within females who had UE infertility, when their thyroid hormone profile was compared with fertile females. This emphasizes that all women with unexplained infertility must be screened for thyroid autoimmunity even if their thyroid profile is within normal range. Our study will help the gynaecologists and endocrinologists to establish diagnosis of thyroid autoimmunity as a baseline investigation in infertile females. More studies

with larger sample size are required for further research and intervention in females having unexplained infertility and an incidence of anti-thyroid antibodies.

## CONCLUSION

In this study, all the subjects had T3, T4, TSH & TBG levels within the normal pre-pregnancy reference range. A trend towards subclinical hypothyroidism and the incidence of anti-thyroid antibodies was observed within females who had UE infertility, when their thyroid hormone profile was compared with fertile females.






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3	Samreen Iqbal	Clinical supervision.	
4	Ghulam Mustafa Khan	Final approval.	
5	Iqra Sohail	Data collection, Write up.	
6	Irum Saddiqa	Statistical analysis.	