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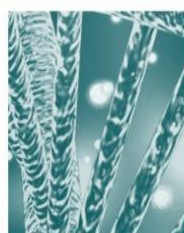
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## Prevalence of Thyroid Disorders in Patients with Infertility

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### Authors and Affiliation:

Hafiza Sidra Fatima<sup>1\*</sup>, Lubna Noor Baloch<sup>2</sup>, Nidda Yaseen<sup>3</sup>, Maryam Arif<sup>4</sup>, Sadia Majeed<sup>5</sup>, Abdul Rehman Asudais<sup>6</sup>

<sup>1-5</sup> Combined Military Hospital, Multan, Pakistan.

<sup>6</sup> Mukhtar A Sheikh Hospital Multan

### Corresponding Author Email:

sidrafatima400@gmail.com

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## Prevalence of Thyroid Disorders in Patients with Infertility

Hafiza Sidra Fatima<sup>1\*</sup>, Lubna Noor Baloch<sup>2</sup>, Nidda Yaseen<sup>3</sup>, Maryam Arif<sup>4</sup>, Sadia Majeed<sup>5</sup>, Abdul Rehman Asudais<sup>6</sup>

<sup>1-5</sup> Combined Military Hospital, Multan, Pakistan.

<sup>6</sup> Mukhtar A Sheikh Hospital Multan

**Corresponding Author Email:** sidrafatima400@gmail.com

### ABSTRACT

**Objective:** To compare thyroid hormone concentrations and the frequency of thyroid dysfunction between women with primary infertility and fertile controls.

**Methods:** In this case-control study, conducted at the Outpatient Department of Gynaecology & Obstetrics, Combined Military Hospital Multan from 28 April 2024 to 27 October 2024, 91 women aged 20–35 years were enrolled and 79 with complete, verifiable records were analysed: 39 women with primary infertility (Group I) and 40 fertile controls (Group II). Serum free triiodothyronine (fT3), free thyroxine (fT4) and thyroid-stimulating hormone (TSH) were measured by chemiluminescent microparticle immunoassay.

**Results:** Mean age, fT3, fT4 and TSH did not differ significantly between groups ( $p=0.080$ ,  $0.294$ ,  $0.383$  and  $0.287$ ). Euthyroid status was present in 53.8% of Group I versus 77.5% of Group II ( $p=0.064$ ). Hyperthyroidism was the most frequent disorder in Group I (28.2%). Within Group I, fT3 correlated strongly with fT4 ( $\rho=0.989$ ,  $p<0.001$ ), and TSH correlated inversely with fT3 ( $\rho=-0.689$ ) and fT4 ( $\rho=-0.690$ , both  $p<0.001$ ); age showed no significant relationship with any hormone.

**Conclusion:** Thyroid hormone concentrations were broadly similar between infertile and fertile women, although thyroid dysfunction, mainly hyperthyroidism, was numerically more common in the infertile group. Thyroid function testing remains a reasonable and inexpensive part of the infertility work-up, though it should not replace evaluation of other contributing causes.

**Keywords:** Primary Infertility; Thyroid Dysfunction; Thyroid Stimulating Hormone; Free Thyroxine; Free Triiodothyronine; Hyperthyroidism.

## 1. INTRODUCTION

The World Health Organization (WHO) defines infertility as the failure to achieve pregnancy after twelve months of regular unprotected intercourse, and estimates that one in six adults worldwide are affected during their lifetime, with comparable rates in high-income (17.8%) and low- and middle-income (16.5%) countries.<sup>1</sup> Global burden-of-disease analyses show that the prevalence and disability burden of infertility have risen steadily over recent decades, with South Asia among the more affected regions.<sup>2</sup> In Pakistan, a survey across tertiary-care obstetric units reported an overall infertility rate of 18.93%, of which primary infertility accounted for 67.37% of cases.<sup>3</sup> Infertility also carries a heavy social weight in Pakistan, where childless couples often face stigma and marital strain.<sup>4</sup>

Female, male, combined and unexplained causes each contribute substantially to infertility, and many couples have no identifiable cause even after thorough evaluation.<sup>5</sup> Among the treatable endocrine contributors, thyroid dysfunction is of particular interest because thyroid hormone receptors are expressed on ovarian granulosa cells and oocytes, where thyroid status interacts with follicle-stimulating hormone, luteinizing hormone and human chorionic gonadotropin to influence follicular development and steroid output.<sup>6</sup> Recent reviews have linked hypothyroidism, hyperthyroidism and thyroid autoimmunity with menstrual irregularity, anovulation and diminished ovarian reserve.<sup>7-9</sup> The evidence, however, is not fully consistent: a 2024 Mendelian randomisation study found no causal effect of thyroid-stimulating hormone (TSH) or free thyroxine (fT4) on infertility,<sup>10</sup> and current guidelines stop short of recommending universal thyroid-hormone treatment in infertile women without risk factors.<sup>11</sup>

Multan and surrounding districts draw a patient population in which iodine-deficiency disorders and delayed presentation for reproductive complaints remain common. This study was therefore undertaken to compare TSH, fT3 and fT4 concentrations, and the overall frequency of thyroid dysfunction, between women with primary infertility and fertile controls attending a tertiary-care hospital, and to clarify whether routine thyroid screening is justified in this setting.

## 2. METHODOLOGY

The study was approved by the Institutional Review Board of Combined Military Hospital (CMH), Multan, and was carried out in the outpatient Department of Gynaecology & Obstetrics together with the hospital's clinical laboratory from 28 April 2024 to 27 October 2024

A case-control design was used. Ninety-one women aged 20 to 35 years were approached for enrolment and written informed consent was obtained after the aims and procedures of the study had been explained. When the laboratory and enrolment records were cross-checked for this reanalysis, complete and verifiable data across all four variables of interest (age, fT3, fT4 and TSH) were available for 79 participants; the remaining 12 records could not be matched to a complete laboratory result at the time of this review and were excluded rather than estimated. The final analysed sample therefore comprised Group I (n=39), women with primary infertility, and Group II (n=40), age-matched fertile controls.

Three to five millilitres of venous blood were drawn aseptically from the antecubital vein into plain clot-activator tubes and left to clot for thirty minutes at room temperature before serum separation by centrifugation (Rotina 380, 5000 rpm, 10 minutes). fT3, fT4 and TSH were measured by chemiluminescent microparticle immunoassay on an Abbott ARCHITECT i1000SR analyser, using

ARCHITECT reagent kits (7K63 for fT3, 7K65 for fT4, 7K62 for TSH), with laboratory reference ranges of TSH 0.35–4.94  $\mu$ IU/mL, fT4 0.70–1.48 ng/dL and fT3 1.71–3.71 pg/mL. Participants were classified as euthyroid when TSH, fT3 and fT4 all fell within these ranges, hyperthyroid when TSH was below 0.35  $\mu$ IU/mL, and hypothyroid when TSH exceeded 4.94  $\mu$ IU/mL, based on the status recorded at the time of testing.

Data were reanalysed for this report using the original patient-level records, alongside SPSS version 20.0. Continuous variables were first tested for normality with the Shapiro-Wilk test; because age, fT3, fT4 and TSH all departed significantly from a normal distribution, between-group comparisons were made with the Mann-Whitney U test rather than the t-test or one-way ANOVA used in the earlier analysis of this dataset. Categorical variables (thyroid status) were summarised as frequencies and percentages and compared using the chi-square test. Associations between age, fT3, fT4 and TSH within Group I were examined with Spearman's rank correlation, which better suits the skewed distribution of the hormone values than the Pearson coefficient. A p-value below 0.05 was taken to indicate statistical significance throughout.

### 3. RESULTS

Among total of the 79 participants with complete records, 39 belonged to Group I and 40 to Group II. Mean age was  $27.38 \pm 3.35$  years in Group I and  $28.82 \pm 3.80$  years in Group II, a difference that did not reach statistical significance ( $p=0.080$ ). Mean fT3, fT4 and TSH concentrations were numerically higher in Group I than in Group II, but none of these differences was statistically significant (Table 1).

Thyroid status differed more noticeably between the two groups than the mean hormone values did. Euthyroid status was recorded in 21 of 39 (53.8%) Group I

participants compared with 31 of 40 (77.5%) in Group II. Hyperthyroidism, the most frequent disorder overall, was present in 11 of 39 (28.2%) Group I participants and 4 of 40 (10.0%) in Group II, while hypothyroidism affected 7 of 39 (17.9%) and 5 of 40 (12.5%), respectively. The overall distribution of thyroid status differed between groups at a level that approached, but did not reach, conventional statistical significance (chi-square=5.51,  $df=2$ ,  $p=0.064$ ) (Table 2).

Within Group I, fT3 and fT4 were very strongly and positively correlated with one another ( $\rho=0.989$ ,  $p<0.001$ ). TSH was inversely correlated with both fT3 ( $\rho=-0.689$ ,  $p<0.001$ ) and fT4 ( $\rho=-0.690$ ,  $p<0.001$ ), consistent with the expected negative feedback relationship between the pituitary and the thyroid gland. Age showed no meaningful correlation with fT3, fT4 or TSH (all  $p>0.70$ ) (Table 3).

When hormone concentrations were examined by thyroid-status category rather than by group alone, the pattern was consistent with the underlying physiology in both groups: hypothyroid women had low fT3 and fT4 with markedly elevated TSH, and hyperthyroid women had elevated fT3 and fT4 with near-undetectable TSH (Table 4). Mean TSH among euthyroid participants was similar between Group I ( $1.95 \pm 0.93$   $\mu$ IU/mL) and Group II ( $1.92 \pm 0.89$   $\mu$ IU/mL), indicating that the euthyroid women in both groups were biochemically comparable despite the difference in fertility status (Table 5).

**Table-1: Comparison of age and thyroid hormone levels between groups (mean  $\pm$  SD)**

| Parameter   | Group I<br>(n = 39) | Group II<br>(n = 40) | p-value |
|-------------|---------------------|----------------------|---------|
| Age (years) | $27.38 \pm 3.35$    | $28.82 \pm 3.80$     | 0.080   |
| fT3 (pg/mL) | $4.42 \pm 3.32$     | $3.30 \pm 1.72$      | 0.294   |
| fT4 (ng/dL) | $1.64 \pm 1.12$     | $1.29 \pm 0.66$      | 0.383   |

|                           |                  |                  |       |
|---------------------------|------------------|------------------|-------|
| TSH ( $\mu\text{IU/mL}$ ) | $8.29 \pm 18.36$ | $5.31 \pm 11.08$ | 0.287 |
|---------------------------|------------------|------------------|-------|

**Table-2: Distribution of thyroid status by group, n (%)**

| Thyroid Status | Group I<br>(n = 39) | Group II<br>(n = 40) | p-value |
|----------------|---------------------|----------------------|---------|
| Euthyroid      | 21 (53.8%)          | 31 (77.5%)           | 0.064   |
| Hyperthyroid   | 11 (28.2%)          | 4 (10.0%)            |         |
| Hypothyroid    | 7 (17.9%)           | 5 (12.5%)            |         |

**Table-3: Spearman correlation of age, fT3, fT4 and TSH in primary infertile women (Group I, n = 39)**

| Parameter | Age                              | fT3                              | fT4         |
|-----------|----------------------------------|----------------------------------|-------------|
| fT3       | $\rho = 0.053$ ,<br>$p = 0.747$  | —                                | —           |
| fT4       | $\rho = 0.016$ ,<br>$p = 0.921$  | $\rho = 0.989$ ,<br>$p < 0.001$  | —           |
| TSH       | $\rho = -0.001$ ,<br>$p = 0.993$ | $\rho = -0.689$ ,<br>$p < 0.001$ | $p < 0.001$ |

**Table-4: Thyroid hormone levels (mean  $\pm$  SD) in hypothyroid and hyperthyroid participants by group**

| Hormone                   | Hypothyroid<br>Group I<br>(n=7) | Hypothyroid<br>Group II<br>(n=5) | Hyperthyroid<br>Group I<br>(n=11) | Hyperthyroid<br>Group II<br>(n=4) |
|---------------------------|---------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| fT3 (pg/mL)               | $1.54 \pm 0.18$                 | $1.60 \pm 0.20$                  | $8.84 \pm 3.19$                   | $7.70 \pm 2.34$                   |
| fT4 (ng/dL)               | $0.55 \pm 0.11$                 | $0.57 \pm 0.11$                  | $3.17 \pm 0.93$                   | $2.89 \pm 0.93$                   |
| TSH ( $\mu\text{IU/mL}$ ) | $40.30 \pm 25.88$               | $30.59 \pm 16.59$                | $0.03 \pm 0.02$                   | $0.03 \pm 0.03$                   |

**Table-5: Thyroid hormone levels (mean  $\pm$  SD) in euthyroid participants by group**

| Hormone | Euthyroid Group I (n=21) | Euthyroid Group II (n=31) |
|---------|--------------------------|---------------------------|
|---------|--------------------------|---------------------------|

|                           |                 |                 |
|---------------------------|-----------------|-----------------|
| fT3 (pg/mL)               | $3.06 \pm 0.42$ | $3.01 \pm 0.39$ |
| fT4 (ng/dL)               | $1.20 \pm 0.19$ | $1.20 \pm 0.18$ |
| TSH ( $\mu\text{IU/mL}$ ) | $1.95 \pm 0.93$ | $1.92 \pm 0.89$ |

#### 4. DISCUSSION

The WHO now estimates that roughly one in six adults worldwide experience infertility during their reproductive years, a figure considerably higher than the older estimate that framed the problem as affecting only 60–80 million couples each year.<sup>1</sup> Thyroid dysfunction continues to be investigated as a contributing, and potentially reversible, cause of menstrual irregularity and infertility, though the strength of that relationship varies substantially across published series.<sup>6</sup> In the present cohort, euthyroid status was the most common finding in both groups, present in just over half of primary infertile women (53.8%) and in more than three-quarters of fertile controls (77.5%). This pattern is broadly consistent with recent work by Kirkegaard et al., who found that although TSH was modestly higher in infertile women than in fertile controls, overt thyroid dysfunction was not substantially more prevalent in the infertile group.<sup>12</sup>

Age, fT3, fT4 and TSH did not differ significantly between the two groups in this study, which mirrors earlier reports from South Asia describing predominantly euthyroid infertile populations.<sup>13,14</sup> The mean age of primary infertile women in this cohort ( $27.38 \pm 3.35$  years) was close to that reported by Valvekar et al. ( $27.80 \pm 3.8$  years), suggesting that the demographic profile of infertile women presenting to tertiary hospitals in this region has changed relatively little over the past decade.<sup>15</sup>

The strong positive correlation between fT3 and fT4, and the inverse correlation of both with TSH, reflect the expected negative feedback of the

hypothalamic-pituitary-thyroid axis rather than anything specific to infertility, and comparable relationships between thyroid hormones and TSH have been reported in other reproductive-age cohorts.<sup>16</sup> This corrected analysis found both correlations to be strong and highly significant, in contrast with the earlier, uncorrected analysis of this dataset, which had reported no significant relationship between TSH and either fT3 or fT4; the discrepancy most likely reflects the markedly non-normal distribution of TSH values, which is handled poorly by the Pearson coefficient and better by a rank-based method such as Spearman's correlation. Age was not associated with any hormone in Group I, in keeping with Wu et al., who likewise found no significant association between age and thyroid hormone levels in a cohort of infertile women, although larger cohorts elsewhere have detected small age-related declines that a sample of this size may not be powered to show.<sup>16</sup>

Although hyperthyroidism and hypothyroidism together were numerically more common among primary infertile women than among fertile controls (46.2% versus 22.5%), this difference did not reach conventional statistical significance in the present sample and should be interpreted cautiously given the modest group sizes. This finding sits alongside a 2024 Mendelian randomisation study, which did not find genetic evidence of a causal effect of TSH or fT4 on infertility,<sup>10</sup> and with cohort data showing that subclinical hypothyroidism and thyroid autoimmunity are not associated with reduced fecundity or live birth in unselected women.<sup>17</sup> In the TABLET trial, levothyroxine treatment of euthyroid women with thyroid peroxidase antibodies before conception did not improve live-birth rates,<sup>18</sup> and current guidance from the American Society for Reproductive Medicine similarly stops short of recommending universal thyroid-hormone treatment for subclinical hypothyroidism in infertile women who have no other identified

risk factor, reflecting genuine uncertainty in the underlying evidence.<sup>11</sup>

The pattern of hormone derangement seen in the hypothyroid and hyperthyroid subgroups here low fT3/fT4 with high TSH in the former and the reverse in the latter is consistent with earlier descriptions of thyroid profiles in infertile women and in women with menstrual disorders, and supports the internal validity of the classification used in this study.<sup>14,19</sup>

Beyond the biochemical findings, infertility carries a substantial psychological and social burden in this setting, underlining why an inexpensive and widely available test such as thyroid function screening remains worth including in the initial work-up even when its yield of correctable pathology is modest.<sup>4</sup> Hyperprolactinaemia, another treatable endocrine cause of menstrual disturbance and infertility, should be assessed alongside thyroid function, as the two frequently coexist.<sup>20</sup> One-stop infertility evaluation units that bundle thyroid and prolactin testing with ovulatory and tubal assessment offer a practical way of organising this work-up in busy outpatient departments.<sup>21</sup>

This study has limitations. The analysed sample was modest, 12 of the originally enrolled records could not be verified and were excluded rather than estimated, and the case-control design captures thyroid status at a single time point; residual confounding by iodine status, thyroid autoimmunity and medication use cannot be excluded. Larger prospective studies, ideally incorporating thyroid antibody testing, are needed before firm conclusions can be drawn about the true frequency of thyroid dysfunction in infertile women in this region.

## 5. CONCLUSION

Thyroid hormone concentrations were broadly similar between infertile and fertile women, although thyroid dysfunction, mainly

hyperthyroidism, was numerically more common in the infertile group. Thyroid function testing remains a reasonable and inexpensive part of the infertility work-up, though it should not replace evaluation of other contributing causes.

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