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EFFECT OF THYROID DISEASES ON SUBFERTILITY

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ABSTRACT

Background: Subfertility refers to a significant reproductive condition that impacts a significant percentage of those women in the world. The thyroid hormones are important in manipulating ovulation, endometrial receptivity, implantation and reproductive functioning in general. Thyroid dysfunction especially hypothyroidism has been increasingly identified as a possible reversible cause of subfertility in women; nevertheless, local data on the effect of thyroid dysfunction is minimal in Pakistan.

Aim: To identify the relationship that exists between thyroid disorders and subfertility in women who visit a tertiary care hospital in Lahore, Pakistan.

Methods: This prospective case-control study was done in the Department of Obstetrics and Gynecology, Gulab Devi Teaching Hospital, Lahore from December 2025 to May 2026. Non-probability consecutive sampling was used to enroll 166 women (83 sub-fertile (cases) and 83 fertile (controls)). Structured interviews were used to collect demographic, clinical and lifestyle data. The chemiluminescent immunoassay of serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) was performed. The SPSS version 27 was used to analyze data with $p \leq 0.05$ was regarded statistically significant.

Results: The mean serum TSH level was significantly higher among sub-fertile women than fertile controls (4.68 ± 2.29 vs. 2.31 ± 1.04 mIU/L, $p<0.001$), whereas FT4 (0.93 ± 0.27 vs. 1.26 ± 0.21 ng/dL, $p<0.001$) and FT3 levels (2.78 ± 0.62 vs. 3.21 ± 0.53 pg/mL, $p<0.001$) were significantly lower. Subclinical hypothyroidism was found in 25.3% of cases and 8.4% of the controls, whereas overt hypothyroidism was found in 12.0% and 2.4%, respectively. After controlling the confounding factors, women who had thyroid disorders were found to be 5 times more likely to be subfertile (Adjusted OR=5.02, 95% CI: 2.39-10.54, $p<0.001$). The highest independent predictors of subfertility were elevated TSH (Adjusted OR=6.74, 95% CI: 2.9115.61, $p<0.001$). Serum TSH levels showed a significant positive relationship with length of subfertility ($r=0.481$, $p<0.001$).

Conclusion: Thyroid disease, especially hypothyroidism, was largely related to subfertility and became a predictor of reproductive impairment by itself. A high concentration of TSH and low concentration of thyroid hormone were closely associated with poor fertility rates. Thyroid screening should be part and parcel of infertility screening to ease the process of identifying and treating abnormalities in thyroids.

KEYWORDS: Subfertility; Thyroid Disorders; Hypothyroidism; Thyroid-Stimulating Hormone; Female Infertility; Reproductive Health; Case-Control Study; Pakistan.

INTRODUCTION

Infertility is one of the major reproductive health issues impacting millions of couples globally and a crucial topic of public health concern on the international scale (Birjandi et al., 2021). According to the estimates made recently, it is believed that the level of infertility among the adult population is about 17.5% worldwide in reproductive age, which highlights the prevalence of the target condition (Unuane et al., 2026). There are several endocrine pathways involved in female fertility out of which thyroid functionality is a very important controller of reproductive physiology. Thyroid hormones aid follicular growth, ovulation, implantation, and early pregnancy maintenance by interactions with the hypothalamic-pituitary-ovarian axis (Amidi et al., 2025). Disturbances in thyroid hormone production may disrupt these physiological processes and adversely affect reproductive outcomes (Thapa et al., 2025). Menstrual abnormalities, ovulatory impairment, and lower fecundity rates in reproductively aged women have been associated with both overt and subclinical thyroid disorders. As a result, there has been a growing interest in research in trying to elucidate the role of thyroid diseases in subfertility and reproductive infertility (Iwase et al., 2026).

The reproductive effects of thyroid hormones are mediated by direct effects on the ovarian tissue and indirect effects via modulation of reproductive endocrine systems (Amidi et al., 2025). Triiodothyronine and thyroxine receptors have been found in granulosa cells, oocytes, and endometrial tissue, which help to confirm the biological significance of

the thyroid in the female reproductive system (Huang et al., 2024). Hypothyroidism may disrupt the gonadotropin-releasing hormone release and raise the level of prolactin in the blood, causing anovulation and menstrual disruptions. Hypothyroid women often manifest as having oligomenorrhea, amenorrhea, and lower conception rates than euthyroid women (Hussain et al., 2025). Hyperthyroidism can also impact negatively the fertility as it changes its sex hormone metabolism and interferes with the usual pattern of secretion of gonadotropin (Arif et al., 2025). A significant percentage of women suffering untreated thyroid disease have been clinically observed to have reproductive dysfunction. This evidence suggests that the thyroid is a vital body part to sustain reproductive competence and the best fertility results (Samantha et al., 2024).

Subclinical hypothyroidism has also become a more significant issue in a list of thyroid disorders due to its fairly high occurrence in women who seek infertility treatment (Munmun et al., 2026). In the population-based studies, it is estimated that subclinical hypothyroidism can occur in 4-8% reproductively aged women globally (Kulkarni et al., 2025). In spite of the fact that circulating thyroxine levels remain within normal levels, high thyroid-stimulating hormone levels can lead to a negative impact on ovarian reserve and reproductive performance (Jalili et al., 2024). Multiple researches have presented increased rates of the occurrence of subclinical hypothyroidism in infertile women compared to their fertile controls (Qiao et al., 2026). Assisted reproductive technology programs have shown some evidence of a relationship between poor thyroid function and reduced implantation and pregnancy rates. Nevertheless, the severity of reproductive impairment due to mild thyroid dysfunction and the usefulness of routine treatment is still controversial. Consequently, additional studies are needed to elucidate the connection between subclinical thyroid disease and subfertility among various populations (Li et al., 2022).

Thyroid diseases and subfertility are especially pertinent to the investigation in Pakistan where infertility is one of the most serious phylogenetic health issues with strong social and psychological implications (Ali et al., 2025). Several elements, including iodine deficiency, differences in nutrition, and lack of access to healthcare in some areas, contribute to the presence of a significant burden of endocrine diseases in Pakistan (Asghar et al., 2025). A study in Pakistan detected hypothyroidism in 28.5% of women who presented with secondary infertility, with 20.8% having subclinical hypothyroidism and 7.7% having overt hypothyroidism (Ehsan et al., 2026). Though these are the results, screening of thyroid is not a consistently involved part of infertility assessment in healthcare centers throughout the country (Rahman et al., 2023). The lack of local evidence in the form of a systematic, extensive investigation restricts the creation of efficient diagnostic and management methods that would suit Pakistani women who undergo subfertility. The differences in socioeconomic status, nutrition and access to healthcare are also likely to affect relationships between thyroid disease and reproductive outcomes among Pakistani citizens. Hence, the current research is warranted to assess how thyroid diseases impact subfertility in Pakistan and to create evidence capable of enhancing the reproductive health services and fertility management practices.

METHODOLOGY

Study Design and Setting

This hospital-based prospective case-control study was conducted in the Department of Obstetrics and Gynecology at Gulab Devi Teaching Hospital, Lahore. The study was carried out from December 2025 to May 2026.

Sample Size and Population

The sample size of this study consisted of 166 participants, with 83 women with the case group and 83 women in the control group. The size of the sample was calculated in terms of a level of significance (5%) and a statistical power (90%) relative to the expected prevalence of hypothyroidism in sub-fertile women (25.2%) and fertile controls (6.9%). The participants were recruited under non-probability consecutive sampling method in which all eligible women who presented during the study period were included in the study till the required sample size was obtained. Those women aged 20-45 years were found to be eligible in the study. The case group included women who had undergone a year or more of subfertility, but the control group comprised fertile women with at least one living-born baby in the past two years with no previous histories of infertility. Those women who had been diagnosed with thyroid disorders prior to the study were excluded. Women who had polycystic ovary syndrome, hyperprolactinemia, or severe underlying illnesses were also excluded to reduce the effects of confounding variables on the fertility outcomes.

Data Collection

There was a prospective collection of data on women who came to the outpatient. The demographic and clinical data were collected as face-to-face interviews with a structured questionnaire after the registration. Data about the age, menstrual history, obstetric and gynecological history, length of subfertility and quality and history of previous medical conditions were documented. Information concerning lifestyle issues such as smoking status, diet and intake of medications known to affect thyroid functions were also recorded on each of the participants.

Laboratory Assessment of Thyroid Function

After the interview process, under aseptic conditions, 5 mL of venous blood was taken out of each of the participants. The blood samples were collected and centrifuged and the serum separated and stored at -20C till analyzed in the lab. The laboratory diagnostic of thyroid functioning involved the determination of serum levels of thyroid-stimulating

hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) by a chemiluminescent immunoassay method in the hospital diagnostic laboratory. To control the quality and reliability of test results, normal internal and external quality assurance processes were observed through the laboratory process. Results of the thyroid function test were compared to the set reference ranges. According to the biochemical results, the participants were classified into euthyroid, hypothyroid and hyperthyroid. The diagnosis of hypothyroidism used serum TSH concentrations of above 4.5 mIU/L with further classification of overt or subclinical based on FT4 levels. The diagnosis of hyperthyroidism was made after the levels of TSH were less than 0.4 mIU/L and further classified into overt and subclinical according to the levels of FT4 and FT3. The association between subfertility and thyroid dysfunction was determined using these classifications.

Data Analysis

Statistical Package of Social Sciences (SPSS) version 27 was used to enter and analyse all the study data. The continuous variables (age, body mass index and subfertility duration) were summarized using the mean and standard deviation. Frequencies and percentages were used to present categorical variables like thyroid status and type of subfertility. Odds ratios (ORs) were computed to measure the association between thyroid disorders and subfertility. The age, body mass index, duration and type of subfertility, smoking, dietary habits and use of medications affecting thyroid functioning was stratified to control possible modifiers of effects. After stratification, odds ratios were re-calculated and the p-value of under 0.05 was used as a statistical significance.

Ethical Considerations

The study was ethically approved by the Institutional Ethical Review Committee of Gulab Devi Teaching Hospital and the College of Physicians and Surgeons Pakistan before the start of data collection. The goals, methods, possible advantages, and voluntary character of the research were clarified to all subjects prior to their enrolment. Each participant was informed through written informed consent, and their personal information was not disclosed to anyone. Participant privacy was safeguarded by the use of unique identification codes, and all data collected were intended to be used in research only.

RESULTS

In the sub-fertile group, the mean age of women was 30.84 ± 4.92 years versus 30.12 ± 4.65 years in the fertile control group with no statistically significant difference between the groups (p=0.334). Likewise, there was no significant difference between the cases and controls in terms of height, weight, BMI, and duration of marriage (p>0.05). Sub-fertile women had a slightly higher mean BMI (26.18 ± 3.92 kg/m^2) compared to controls (25.02 ± 3.51 kg/m^2), which was almost statistically significant (p=0.052).

Table 1. Demographic Characteristics of Study Participants

Variable	Cases (n=83) Mean ± SD	Controls (n=83) Mean ± SD	p-value
Age (years)	30.84 ± 4.92	30.12 ± 4.65	0.334
Height (cm)	159.74 ± 5.82	160.26 ± 5.67	0.559
Weight (kg)	66.85 ± 10.21	64.41 ± 9.76	0.118
BMI (kg/m²)	26.18 ± 3.92	25.02 ± 3.51	0.052
Duration of Marriage (years)	5.92 ± 2.31	5.68 ± 2.14	0.488

The mean years of subfertility were 3.74 ±1.61 years among the 83 women who were sub-fertile. In 54 (65.1%) participants primary subfertility was found, and 29 (34.9%) participants had secondary subfertility. Cases 16.9% and controls 10.8% reported smoking, but the difference was not significant (p=0.255). In a similar way, there were also no significant differences in dietary habits and medications that can influence thyroid functions in the groups (p>0.05). These results indicate that lifestyle-related variables were more or less equal in the cases and controls.

Table 2. Baseline Clinical Characteristics of Study Participants

Variable	Cases (n=83)	Controls (n=83)	p-value
Duration of Subfertility (years) Mean ± SD	3.74 ± 1.61	—	—
Primary Subfertility	54 (65.1%)	—	—
Secondary Subfertility	29 (34.9%)	—	—
Current Smokers	14 (16.9%)	9 (10.8%)	0.255
Non-Smokers	69 (83.1%)	74 (89.2%)	
Vegetarian Diet	18 (21.7%)	15 (18.1%)	0.563
Mixed Diet	65 (78.3%)	68 (81.9%)	
Use of Medications Affecting Thyroid Function	11 (13.3%)	6 (7.2%)	0.199

No Such Medication Use	72 (86.7%)	77 (92.8%)	

There was a significant difference in the parameters of thyroid functions in sub-fertile women and fertile controls. Mean serum TSH level between cases (4.68 ± 2.29 mIU/L) and controls (2.31 ± 1.04 mIU/L) also varied significantly ($p<0.001$). Conversely, mean FT4 and FT3 concentrations were significantly lower among sub-fertile women compared with fertile controls (FT4: 0.93 ± 0.27 vs. 1.26 ± 0.21 ng/dL; FT3: 2.78 ± 0.62 vs. 3.21 ± 0.53 pg/mL; $p<0.001$ for both). These results imply that there is a close relation between thyroid dysfunction and subfertility.

Table 3. Thyroid Function Test Results

Variable	Cases (n=83) Mean ± SD	Controls (n=83) Mean ± SD	p-value
Serum TSH (mIU/L)	4.68 ± 2.29	2.31 ± 1.04	0.00019
Free T4 (ng/dL)	0.93 ± 0.27	1.26 ± 0.21	0.00088
Free T3 (pg/mL)	2.78 ± 0.62	3.21 ± 0.53	0.00047

Of the sub-fertile women, 45 (54.2%) were euthyroid and 71 (85.5%) fertile controls. Subclinical hypothyroidism was present in 21 (25.3%) cases and 7 (8.4%) controls only indicating a significant association with subfertility (OR=4.73, 95% CI=1.8811.89, $p<0.001$). Overt hypothyroidism was also significantly more prevalent among cases (12.0%) than controls (2.4%) (OR=7.89, 95% CI=1.65–37.67, p=0.002). Hyperthyroid disorders were also more common in sub-fertile women although these associations were not statistically significant.

Table 4. Distribution of Thyroid Status among Cases and Controls

Thyroid Status	Cases (n=83)	Controls (n=83)	OR (95% CI)	p-value
Euthyroid	45 (54.2%)	71 (85.5%)	Reference	—
Subclinical Hypothyroidism	21 (25.3%)	7 (8.4%)	4.73 (1.88–11.89)	<0.001
Overt Hypothyroidism	10 (12.0%)	2 (2.4%)	7.89 (1.65–37.67)	0.002
Subclinical Hyperthyroidism	5 (6.0%)	2 (2.4%)	3.94 (0.74–20.89)	0.092
Overt Hyperthyroidism	2 (2.4%)	1 (1.2%)	3.16 (0.28–35.78)	0.384

It was observed that age, height, weight, BMI, period of marriage, FT4 and FT3 had an approximate normal distribution ($p>0.05$). Nonetheless, subfertility time and serum TSH levels had significant non-normality ($p<0.05$). In turn, non-parametric tests were used where the appropriate, specifically when it comes to TSH analysis, whereas the parametric tests were conducted when the variables were normally distributed.

Table 5. Normality Assessment of Continuous Variables Using Shapiro-Wilk Test

Variable	W Statistic	p-value
Age (years)	0.982	0.076
Height (cm)	0.987	0.118
Weight (kg)	0.979	0.063
BMI (kg/m²)	0.975	0.051
Duration of Marriage (years)	0.984	0.089
Duration of Subfertility (years)	0.962	0.008
Serum TSH (mIU/L)	0.893	<0.001
Free T4 (ng/dL)	0.977	0.058
Free T3 (pg/mL)	0.981	0.071

Based on stratification, the association of thyroid disorders with subfertility did not change significantly in most categories. Women with BMI ≥25 kg/m² demonstrated the strongest association (OR=8.34, 95% CI=2.56–27.11, $p<0.001$). There were also significant relationships between smokers (OR=6.30, p=0.032), women over 30 years of age (OR=5.83, $p<0.001$) and women who adhered to mixed dietary patterns (OR=4.97, $p<0.001$). These results suggest that the association between thyroid dysfunction and subfertility remained even after adjusting the effects of significant confounding variables.

Table 6. Stratification Analysis for Potential Effect Modifiers

Variable	Cases with Thyroid Disorder n/N (%)	Controls with Thyroid Disorder n/N (%)	OR (95% CI)	p-value
Age ≤30 years	18/39 (46.2%)	7/43 (16.3%)	4.42 (1.64–11.91)	0.001
Age >30 years	20/44 (45.5%)	5/40 (12.5%)	5.83 (1.95–17.41)	0.00037
BMI <25 kg/m²	15/34 (44.1%)	8/41 (19.5%)	3.26 (1.18–9.00)	0.015
BMI ≥25 kg/m²	23/49 (46.9%)	4/42 (9.5%)	8.34 (2.56–27.11)	0.00082
Smokers	9/14 (64.3%)	2/9 (22.2%)	6.30 (1.01–39.20)	0.032
Non-Smokers	29/69 (42.0%)	10/74 (13.5%)	4.65 (2.02–10.73)	0.00014
Vegetarian Diet	10/18 (55.6%)	3/15 (20.0%)	5.00 (1.02–24.49)	0.030
Mixed Diet	28/65 (43.1%)	9/68 (13.2%)	4.97 (2.07–11.93)	0.00091
Medication Use	8/11 (72.7%)	2/6 (33.3%)	5.33 (0.73–38.88)	0.072
No Medication Use	30/72 (41.7%)	10/77 (13.0%)	4.79 (2.09–10.97)	0.00056

After age, BMI, smoking, dietary habits, duration of subfertility and taking of medicines were adjusted, thyroid disorders were still found to be significantly attributed to subfertility. Thyroid dysfunction women showed a 5-fold increased risk of subfertility as compared to women with no thyroid disorders (Adjusted OR=5.02, 95% CI=2.3910.54, p<0.001). This result corroborates the fact that thyroid dysfunction is its own predictor of subfertility.

Table 7. Post-Stratification Association between Thyroid Disorders and Subfertility

Variable	Cases (n=83)	Controls (n=83)	Adjusted OR	95% CI	p-value
Presence of Thyroid Disorder	38 (45.8%)	12 (14.5%)	5.02	2.39–10.54	0.00028
Absence of Thyroid Disorder	45 (54.2%)	71 (85.5%)	Reference	—	—

Multivariate logistic regression determined high TSH serum levels to be the best independent predictor of subfertility (Adjusted OR=6.74, 95% CI=2.9115.61, p<0.001). Subfertility was also strongly linked with lower FT4 concentrations and odds ratio was more than four times higher (OR=4.18, p=0.001). Equally, low levels of FT3 also predicted subfertility (OR=2.91, p=0.011) independently. Statistical significance after adjustment (OR=2.42, P=0.028) was still contributed by increased BMI even after adjustment, whilst smoking, age over 30 years and medication use did not remain significant. These results illustrate that abnormalities in thyroid hormones, especially high levels of TSH, had an independent effect on subfertility.

Table 8. Multivariable Logistic Regression Analysis of Factors Associated with Subfertility

Variable	Adjusted OR	95% CI	p-value
Elevated TSH (>4.5 mIU/L)	6.74	2.91–15.61	0.00063
Reduced FT4 (<0.8 ng/dL)	4.18	1.79–9.75	0.001
Reduced FT3 (<2.5 pg/mL)	2.91	1.28–6.62	0.011
BMI ≥25 kg/m²	2.42	1.10–5.34	0.028
Smoking	2.11	0.91–4.89	0.078
Age >30 years	1.56	0.77–3.18	0.215
Medication Affecting Thyroid Function	1.84	0.61–5.53	0.279

It was established that serum TSH level was significantly positively correlated with the length of subfertility (r=0.481, p<0.001), such that women who had higher levels of TSH were more likely to have a longer duration of subfertility. On the contrary, FT4 and FT3 had remarkable negative significant correlations with duration of subfertility (r=-0.393 and r=-0.287, respectively). A robust inverse relationship between TSH and FT4 (r=-0.618) and TSH and FT3 (r=-0.529) was found which validated the anticipated physiological association between thyroid hormones. These results

also confirm the hypothesis, that progressive thyroid dysfunction is proportionate to progressive reproductive impairment in sub-fertile women.

Table 9. Correlation Analysis between Thyroid Parameters and Duration of Subfertility

Variable Pair	Correlation Coefficient (r)	95% CI	p-value
Duration of Subfertility vs TSH	+0.481	0.295–0.627	0.00074
Duration of Subfertility vs FT4	-0.393	-0.556 to -0.194	0.381
Duration of Subfertility vs FT3	-0.287	-0.475 to -0.076	0.008
TSH vs FT4	-0.618	-0.736 to -0.464	0.00067
TSH vs FT3	-0.529	-0.670 to -0.348	0.00032

DISCUSSION

The objective of the current study was to identify the correlation between thyroid diseases and subfertility among women. One of the key findings of this research was the greatly distorted profile of thyroid hormone among the sub-fertile women, as opposed to those who are fertile. The incidence of mean TSH concentration of cases of 4.68 ± 2.29 mIU/L was considered to be of very great significance compared to that of controls of 2.31 ± 1.04 mIU/L ($p<0.001$). In contrast, mean FT4 levels were significantly lower among cases (0.93 ± 0.27 ng/dL) than controls (1.26 ± 0.21 ng/dL), while FT3 levels were 2.78 ± 0.62 pg/mL and 3.21 ± 0.53 pg/mL, respectively ($p<0.001$). These results confirm the biological hypothesis, that the inadequate availability of thyroid hormones has a negative impact on ovulatory, endometrial receptivity and implantation potential. The same findings were expressed by Jagun et al., (2022) who reported significant higher levels of TSH in the infertile women with the mean levels being 1.8 times higher than in fertile controls (Jagun et al., 2022). Zhao et al. (2022) conducted a research on 438 infertile women and discovered that during assisted reproductive treatment, implantation and pregnancy rates were low in patients whose TSH levels are high (Zhao et al., 2022). Moreover, Zhang et al. (2024) found that even moderate changes in TSH could interfere with reproductive endocrinology due to changes in the secretion of gonadotropin and ovarian responsiveness (Zhang et al., 2024). In turn, the current results are additional reasons to think that thyroid dysfunction shall significantly contribute to the poor female fertility.

The prevalence of thyroid diseases also emphasized the role of hypothyroidism as an etiological factor of subfertility. The prevalence rate of subclinical hypothyroidism was 25.3% in sub-fertile women versus 8.4% in controls with odds ratio of 4.73 (95% CI: 1.8811.89; p=.001). Overt hypothyroidism was observed in 12.0% of cases and 2.4% of controls, corresponding to an odds ratio of 7.89 (95% CI: 1.65–37.67; p=0.002). By way of generalizing, thyroid dysfunction was reported to be 45.8% compared to 14.5% of the controls indicating that the burden is significantly higher among sub-fertile women. These results are in close correlation with those of Rao et al. (2020), who came up with an approximately 44% incidence of thyroid abnormalities in infertile women versus 15% in fertile women (Rao et al., 2020). Likewise, Ali et al. (2025) recorded prevalence rates of subclinical hypothyroidism between 20% and 27% in women with a presentation of infertility which are astonishingly high compared to the present study (Ali et al., 2025). The dominance of subclinical hypothyroidism substantiates earlier claims that mild thyroid malfunction could be a functional limitation to reproduction despite having no apparent clinical manifestations. So, regular thyroid screening could be a beneficial part of infertility assessment.

The stratification analysis revealed that the relationship between thyroid dysfunction and subfertility remained when various possible confounding factors were accounted. The most significant relationship between thyroid disorders and subfertility was seen with women having BMI 25kg/m 2+ with odds ratio of 8.34 (95%, CI: 2.5627.11) p=0.001. Significant associations were also observed among women older than 30 years (OR=5.83; 95% CI: 1.95–17.41; $p<0.001$) and among smokers (OR=6.30; 95% CI: 1.01–39.20; p=0.032). Nevertheless, the presence of thyroid dysfunction in almost all strata was highly correlated with subfertility, indicating that the relationship is not only accounted by lifestyle and anthropometric factors. These results are also aligned with those of Shilpakar et al. (2025), who indicated that obesity and increasing age of reproductive capability can also lead to the further worsening of thyroid related reproductive dysfunction via complicated metabolic and endocrine mechanisms (Shilpakar et al., 2025). Equally, Liu et al. (2024) established that women who had high BMI and thyroid abnormalities were found to have very poor reproductive outcomes than euthyroid women with normal BMI (Liu et al., 2024). The association of considerable strengths persists after stratification supports the assumption that thyroid dysfunction is an independent reproductive risk factor. Therefore, screening measures must not be limited to the particular demographic subgroups but include all women with subfertility.

Multivariate logistic regression analysis revealed that elevated TSH was the best independent variable predicting subfertility in the study sample. Females who had TSH levels above 4.5 mIU/L had odds ratio of 6.74 that were greater than those of women with intact thyroid functions (95% CI: 2.9115.61; $p<0.001$). Reduced FT4 levels independently increased the odds of subfertility by more than four times (OR=4.18; 95% CI: 1.79–9.75; p=0.001), while reduced

FT3 levels nearly tripled the risk (OR=2.91; 95% CI: 1.28–6.62; p=0.011). Such results suggest that dysfunctions along the hypothalamic-pituitary-thyroid axis are one of the causes of reproductive malfunction. Likewise, Aliu-Ayo et al. (2023) found that high TSH levels were some of the most consistent endocrine predictors of infertility in a variety of observational studies including more than 5,000 women. Also, it was shown that women who had higher TSH levels had a drastically lower clinical pregnancy rate following least case of assisted reproduction (Aliu-Ayo et al., 2023). The size of the odds ratios determined in the current research highlights clinical importance of thyroid function tests in the process of fertility assessment. Thus, treatment of thyroid abnormality can provide a valuable chance to enhance the reproduction of these women.

The correlation analysis also provided further support of a biologically significant correlation between thyroid dysfunction and reproductive impairment. Subfertility duration positively correlated with TSH serum levels (r=0.481, p<0.001) with higher levels of TSH being linked to longer reproductive impairment. On the other hand, it was found that there were significant negative correlations between duration of subfertility and FT4 (r=-0.393, p=0.001) and FT3 (r=-0.287, p=.008). Good negative correlations were also found between TSH and FT4 (r=-0.618, p<0.001) and between TSH and FT3 (r= -0.529, p<0.001), which were expected physiological feedback. These results are corroborated by Mansuri et al. (2020), who indicated that progressive declines in ovarian reserve indicators and reproductive performance were linked to worsening thyroid dysfunction (Mansuri et al., 2020). Similarly, Wu et al. (2021) showed that thyroid hormone receptors (expressed in the ovarian and endometrial tissues) directly contribute to the follicular maturation and implantation. The existing findings thus indicate that thyroid abnormalities not just predispose the risk of subfertility, but also may influence its continuation (Wu et al., 2021). Altogether, the results are an interesting piece of evidence that thyroid dysfunction, especially hypothyroidism is a significant and possibly alterable risk factor of female subfertility.

This study has a few limitations that should be discussed. To start with, the research was carried out at one tertiary care hospital which could limit the extrapolation of the findings to the entire Pakistani population. Second, the sample size was relatively small (n=166), which might have diminished the statistical power to identify all the associations with less prevalent thyroid disorders, with hyperthyroidism. Third, the case-control design was used so as to identify the associations but not a definite causal relation between thyroid dysfunction and subfertility. Fourth, thyroid autoantibodies were not tested, and thus it was not possible to evaluate the possible role of thyroid autoimmunity in reproductive impairment. Also, some data about lifestyle factors were self-reported, and it could be biased by recall. Further research with bigger sample sizes, longitudinal follow-ups, and a thorough evaluation of autoimmunity in the thyroid is suggested in future multicenter experiments to better define the connection between thyroid disorders and female reproductive success.

CONCLUSION

Thyroid dysfunction has been shown to be significantly related to subfertility in women of reproductive age, as demonstrated in this study. Women with sub-fertilities had considerably high serum TSH level (4.68 2.29 mIU/L vs. 2.31 1.04 mIU/L, p<0.001) and less FT4 and FT3 level than women who were fertile controls. Subclinical hypothyroidism was more common with sub-fertile women (25.3% vs. 8.4%), as well as was overt hypothyroidism (12.0% vs. 2.4%), which demonstrated that hypothyroidism was the thyroid disease most related with the impaired fertility. The multivariate analysis showed that high TSH predicted subfertility by itself, with odds ratio of 6.74 (95% CI: 2.91 -15.61, p<0.001), a clinical implication of TSH as a predictor of reproductive dysfunction. Additionally, there are positive associations between the TSH level and the years of subfertility indicating that deteriorating thyroid dysfunction can be the cause of not only the development but also maintenance of fertility issues. These results support the rationale of regular testing of thyroid functioning in the female population with subfertility and justify the inclusion of thyroid screening in the programs of testing fertility to make it possible to identify the problem early and provide the patient with proper treatment.

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