

THYROID DYSFUNCTION AND MENSTRUAL IRREGULARITIES IN INFERTILE WOMEN: A COMPARATIVE ANALYSIS OF HORMONAL PROFILES

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Abstract

Infertility, defined as the inability to conceive after ≥ 12 months of unprotected intercourse, affects 5–15% of couples globally, with thyroid dysfunction increasingly recognized as a contributor to reproductive impairment. Thyroid hormones (T3, T4) and thyroid-stimulating hormone (TSH) regulate ovarian function, follicular development, and endometrial receptivity, with imbalances linked to menstrual irregularities, ovulatory dysfunction, and implantation failure. This case-control study investigated thyroid profiles and menstrual patterns in 100 married women (18–55 years), categorized into primary infertility ($n=40$), secondary infertility ($n=10$), and controls ($n=50$). Blood samples were analyzed via chemiluminescence immunoassay (CLIA) for T3, T4, and TSH, and menstrual regularity was assessed through clinical histories.

Menstrual irregularities were significantly more prevalent in infertile groups: 62.5% of primary infertility cases exhibited oligomenorrhea (15/40) or amenorrhea (10/40), and 80% of secondary infertility cases reported oligomenorrhea (7/10), compared to 88% regular cycles in controls. Thyroid analysis revealed comparable T3 levels across groups (controls: 6.16 ± 1.63 ; primary: 6.41 ± 2.81 ; secondary: 6.14 ± 2.81 ; $p=0.812$). T4 levels were numerically lower in infertility groups (19.17 ± 8.09) versus controls (22.41 ± 5.77 ; $p=0.354$), while TSH levels were elevated in infertility groups (4.47 ± 1.59) compared to controls (3.11 ± 1.48 ; $p=0.69$), though neither reached statistical significance. The findings underscore a high prevalence of menstrual irregularities in infertile women and suggest trends toward subclinical thyroid dysfunction, particularly elevated TSH, which may disrupt reproductive physiology.

INTRODUCTION

Infertility can be defined as the inability to become pregnant after a minimum of 12 months of frequent, unprotected sex and affects an estimated 5–15% of married couples globally (1). There is a firmly established relationship between thyroid function and

female fertility; pregnancy exerts a significant influence on thyroid gland function, whereas thyroid disease has strong links with female infertility (2). It has demonstrable influences upon both pregnancy and fetal outcomes with evident effects on both

pregnancy and fetal outcomes (3). It can be divided into two categories: primary infertility is used to describe couples who have never been able to conceive, and secondary infertility is used for those who were previously able to become pregnant but cannot now (4). The thyroid gland is a butterfly shaped organ made up of bulbous right and left lobes joined in the midline by a thin piece called the isthmus. Situated in the neck, the thyroid encircles the anterior trachea directly below the larynx at the level of vertebrae C5–T1. It is approximately 5 cm tall, 5 cm wide, and 20–30 g in weight in adults, with the female thyroids being slightly heavier (5). The thyroid gland releases three hormones: thyroxine (T4) and triiodothyronine (T3), both of iodinated tyrosine origin, and calcitonin, a polypeptide hormone. Follicular cells secrete T4 and T3, whereas the secretion of calcitonin takes place from cells of varying embryonic origin, C cells. Calcitonin's role is negligible in maintaining calcium homeostasis, but the disturbances of its secretion are not frequent. Secretory disturbances of T4 and T3 are frequent. The gland releases large amounts of T4, with some of the T4 converted by peripheral tissues to more active T3. Thyroid hormone synthesis is stimulated by thyrotropin-stimulating hormone (TSH) in the pituitary gland and suppressed by hypothalamic thyrotropin-releasing hormone. T4 and T3 provide negative feedback inhibition of TSH secretion. These hormones are required for the proper growth, development, and metabolism of metabolic processes. The best assessment of thyroid function is by determining plasma fT4 and TSH levels with the measurement of T3 if hyperthyroidism is suspected (6). In hypothyroidism, fT4 is reduced with increased TSH, whereas in hyperthyroidism, TSH is reduced and fT3 and fT4 are increased (7). The prevalence of thyroid disorders is increasing worldwide, probably due to increased awareness and diagnosis. It is more common in the 20–45 years age group. The prevalence of subclinical hypothyroidism (SCH) is 5–7%, overt hypothyroidism is 2–4.5%, hyperthyroidism is 0.5–1%, and thyroid autoimmunity (TAI) is 5–10% (8).

Thyroid hormones are important for female reproductive health through the regulation of metabolism and maintenance of ovarian and uterine tissue development (9). They are necessary for

follicular development, fertilization, embryogenesis, and implantation (10). Normal menstrual cycles rely on well-coordinated signaling in the hypothalamic-pituitary-ovarian axis, which can be disturbed by alterations in thyroid or ovarian function, leading to ovulatory dysfunction and menstrual irregularities (11).

The hypothalamic-pituitary-thyroid and hypothalamic-pituitary-ovarian axes interact in a highly complex and bidirectional manner. Thyroid function can affect ovarian activity, and ovarian function has the potential to affect thyroid control (12, 13). In particular, FSH and T3 interactions have been found to operate synergistically to enhance granulosa cell activity and inhibit programmed cell death or apoptosis (14).

The ovarian cycle timing depends on the coordinated action of growth factors and hormones to facilitate follicular maturation (15). T4 and T3 control follicular growth and atresia by modulating thyroid hormone receptors on the granulosa, cumulus oophores, and ovarian stromal cells (16–18). TSH receptor expression in ovarian tissue is positively controlled by FSH and negatively controlled by estradiol, again demonstrating intricate hormonal crosstalk (19). Luteinized granulosa cells contain deiodinases 2 and 3, which are pivotal enzymes in the metabolism of thyroid hormones. Follicle-stimulating hormone (FSH) stimulates the proliferation of granulosa cells, whereas triiodothyronine (T3) stimulates proliferation through the PI3/Akt pathway and inhibits apoptosis. Thyroid-stimulating hormone (TSH) receptors are also present in the ovarian tissue, and their expression is increased by FSH and suppressed by estradiol, thus demonstrating the close interplay between thyroid and reproductive hormones. Thyroid hormone receptors ($\alpha 1$, $\beta 1$, and $\beta 2$) are also found in oocytes, granulosa cells, and cumulus cells, allowing thyroid hormones to directly affect follicular growth and development.

Thyroid hormone receptors have also been identified on the surface of the endometrium, where they are key in enabling communication between the endometrium and blastocyst, thus controlling endometrial receptivity and the timing of the window period of implantation (19–21). The endometrium contains two unique isoforms of thyroid hormone receptors, alpha and beta, which are coded by two independent genes with $\alpha 1$ and $\beta 1$ receptors and the

TSH receptor. These proteins are maximally expressed at the time of receptive endometrium 23 and in the mid-secretory phase of the menstrual cycle (22). By implantation, TSH causes upregulation of leukemia inhibitory factor (LIF) and its receptor (LIFR) in endometrial epithelial cells, such as Ishikawa cells (23, 24). TSH increases the expression of glucose transporter 1 (GLUT-1) and increases the absorption of glucose to meet the energy requirements of the implanting embryo. TSH also enhances the expression of glucose transporter 1 (GLUT-1) and facilitates glucose uptake (25, 26).

The most common causes of female infertility are ovulatory disorders such as polycystic ovary syndrome (PCOS), hypothalamic dysfunction, and premature ovarian insufficiency; pelvic inflammatory disease (PID) resulting in tubal damage; endometriosis in which the uterine-like tissue grows outside the uterus involving ovaries and tubes; and advanced maternal age. decreased ovarian reserve; environmental and occupational exposure to chemicals and toxins; congenital abnormalities of the reproductive tract, and hormonal imbalances such as thyroid dysfunction. Other contributing causes are uterine abnormalities, such as polyps and fibroids, cervical mucus issues, and habit-related causes, such as stress, dramatic weight changes in the body, and excessive physical activity. The causes interfere with ovulation, fertilization, or implantation, and thus compromise fertility (27).

After puberty, hyperthyroidism often causes infrequent and scanty menstrual periods and may lead to amenorrhea (absence of menstruation). In contrast, hypothyroidism typically results in menstrual cycles that are too frequent and heavy, sometimes with prolonged bleeding that can cause anemia. It can also cause oligomenorrhea, amenorrhea, polymenorrhagia, menorrhagia, diminished libido, and failure to ovulate. Both hyperthyroidism and hypothyroidism significantly affect estrogen and androgen metabolism, menstrual function, and fertility, often leading to menstrual irregularities and reduced reproductive capability. These hormonal imbalances can disrupt ovulation and menstrual cycle, contributing to infertility (28).

MATERIAL AND METHODS

This case-control study was conducted at Chaudhary Muhammad Akam Hospital, Lahore, from October 2024 to February 2025. Initially, 150 infertile subjects were examined, comprising both primary and secondary infertility cases. From these, 95 subjects were selected based on the inclusion or exclusion criteria, and 50 of them consented to participate in the study, forming the infertile group. Concurrently, a control group was allocated from 100 examined subjects, out of which 50 were selected who gave consent to participate. The final sample thus included two groups, 50 infertile women and 50 controls, for the analysis of thyroid hormone levels and their association with infertility. Participants were selected based on a detailed history and laboratory investigation.

Infertile women aged between 20 and 55 years with a marriage duration of more than one year. Female infertility factors, including tubal issues, congenital urogenital anomalies, or organic lesions, were also considered for patient inclusion. Detailed history, including age and menstrual history, was obtained. Patients taking medications such as amiodarone and phenytoin or having a known history of thyroid disorders were excluded from the study.

We collected the blood samples in a sterile yellow-top container utilizing a routine venipuncture technique, and the serum was kept separated from red cells. Serum was separated from blood using centrifugation. Specimens that could not be tested immediately were refrigerated at 2-8°C.

Thyroid profiles (T3, T4, TSH) were estimated using a Chemiluminescence Immunoassay (CLIA) automated instrument. Normal thyroid function was defined as follows: T3 (4.26–8.1 pm/L), T4 (10.0–28.2 pm/L), and TSH (0.5–5.0 mIU/L). Data analysis was performed using Microsoft 365 and SPSS.

RESULTS

Table 1 summarizes participant characteristics in a study involving 100 married females, divided into three groups: 40 with primary infertility (unable to conceive), 10 with secondary infertility (unable to conceive again after prior pregnancy), and 50 controls. Participants aged 18–55 years were categorized according to menstrual patterns: 61 had regular cycles, 28 had infrequent cycles (oligomenorrhea), and 11

had absent cycles (amenorrhea). This study exclusively included married women.

Table 1: Demographic Characteristics of the Study Participants

Variables	Characteristics
Infertility Groups	Primary infertility (40) Secondary infertility (10)
Age (years)	Control (50) 18-55 years
Menstrual pattern	Regular (61) Oligomenorrhea (28) Amenorrhea (11)
Gender	Married female only

Menstrual Pattern in Study Group

The mean age was 29.70 ± 5.87 years in the control group, 27.78 ± 6.47 years in the primary infertility group, and 27.95 ± 5.43 years in the secondary infertility group. Regular menstrual cycles were the most common in the control group (44 women), followed by primary infertility (14) and secondary infertility (2) (Table 2). Oligomenorrhea was reported

in 15 primary infertility cases, 7 secondary infertility cases, and 6 controls. Amenorrhea was seen in 10 women with primary infertility and 2 with secondary infertility, while no cases of amenorrhea were reported in the control group. These findings highlight that menstrual irregularities, such as oligomenorrhea and amenorrhea, were more frequent in infertile women than in healthy controls.

Table 2: Menstrual Pattern in Study Group

Variables	Control group	Primary infertility	Secondary infertility
Age	29.70 ± 5.87	27.78 ± 6.47	27.95 ± 5.43
Regular	44	14	2
Oligomenorrhea	6	15	7
Amenorrhea	0	10	2

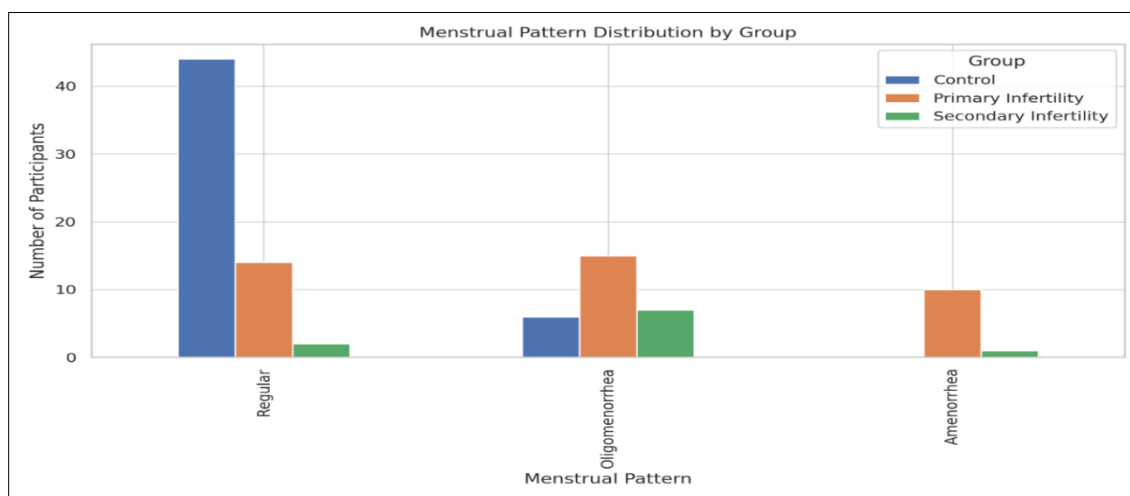


Figure 1: Menstrual Pattern Distribution by Group

Overall Evaluation of Study Participants

Table 2 and Figure 1 show that regular menstrual cycles were most common in the control group (44 women), followed by primary infertility (14) and secondary infertility (2). Oligomenorrhea was reported in 15 primary infertility cases, 7 secondary infertility cases, and 6 controls. Amenorrhea was seen in 10 women with primary infertility and 1 with secondary infertility, while no cases of amenorrhea were reported in the control group. These findings highlight that menstrual irregularities, such as oligomenorrhea and amenorrhea, were more frequent in infertile women than in healthy controls.

Age Distribution by Group

Table 3 and Figure 2 show the age distribution by each group. Most participants were within the 22–40 years age range. The control group showed a wider and more even age distribution, with a peak around 33–36 years. The primary infertility group was more widespread, with visible counts across many age groups. The secondary infertility group was more concentrated in the 26–40 years range. The age distribution was fairly balanced, with no extreme outliers across the groups.

Table 3: Age Distribution by Group

Infertility Groups	N	Mean± SD
Primary Infertility	40	27.78±6.47
Secondary Infertility	10	27.95±5.43
Control	50	29.70±5.87
Total	100	28.76±6.09

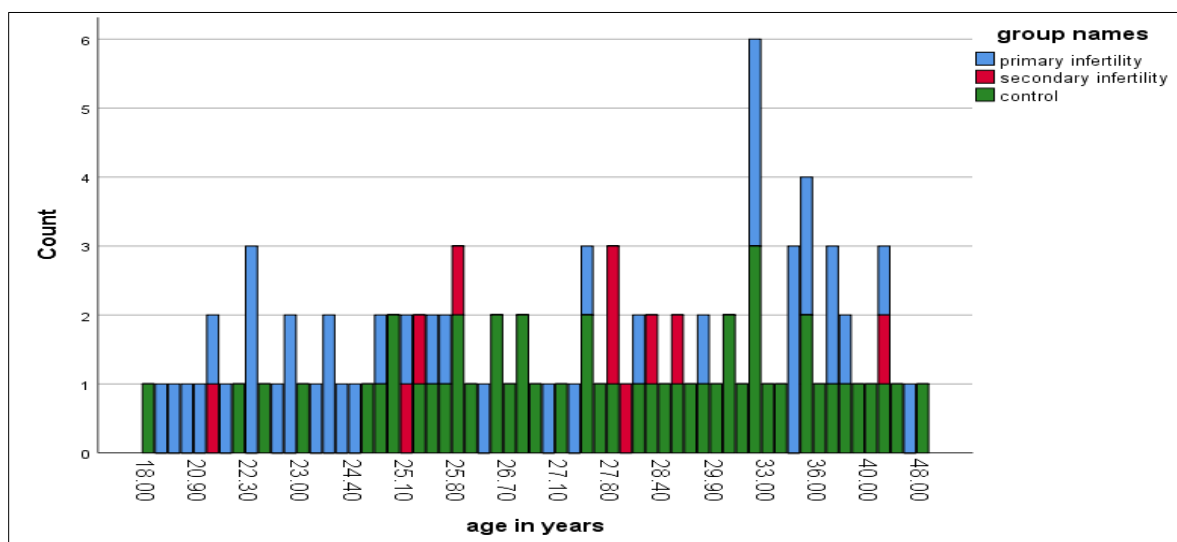


Figure 2: Age Distribution by Group

Percentage Distribution of Menstrual Pattern

Table 4 and Figure 3 show the percentage distribution of menstrual patterns within each group. The control group consisted of 61 (61%) mostly regular cycles. The primary infertility group included a balanced mix of

oligomenorrhea 28 (28%) and amenorrhea 11 (11%), with fewer regular cycles, while the secondary infertility group included mostly oligomenorrhea, with very few regular cycles and one case of amenorrhea.

Table 4: Percentage Distribution of Menstrual Pattern

Menstrual pattern	Frequency	Percentage (%)
Regular	61	61.0%
Oligomenorrhea	28	28.0%
Amenorrhea	11	11.0%
Total	100	100.0%

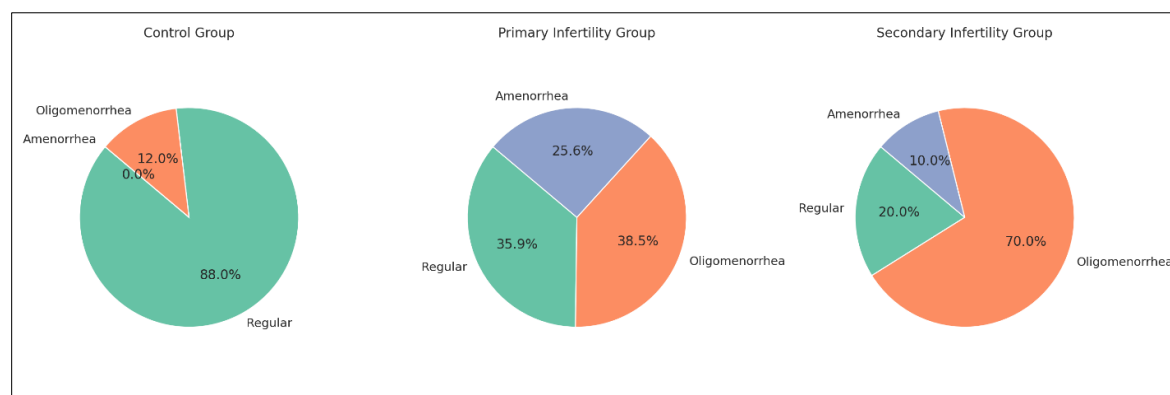


Figure 3: Percentage Distribution of Menstrual Patterns

Table 5: Biochemical Evaluation of the Study Participants

Variables	Control group	Primary infertility	Secondary infertility	F	P-value
N	50	40	10		
T3	6.16±1.63	6.41±2.81	6.14±2.81	0.209	0.812
T4	22.41±5.77	19.17±8.09	19.17±8.09	1.049	0.354
TSH	3.11±1.48	4.47±1.59	4.47±1.59	2.743	0.69

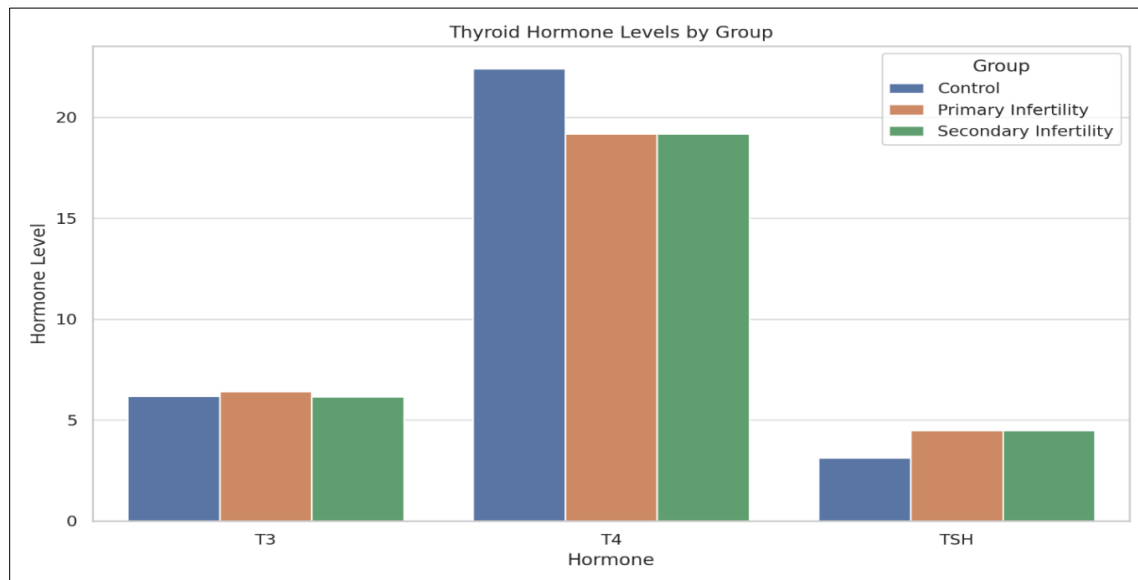


Figure 4: Thyroid Hormone Level by Group

Table 5 and Figure 4 provide a comparative analysis of thyroid hormone profiles, T3, T4, and TSH across three participant groups: 50 controls, 40 individuals with primary infertility, and 10 individuals with secondary infertility. The values are presented as mean \pm standard deviation, with F-statistics and p-values derived from ANOVA to evaluate group differences. For T3, the mean levels were comparable among all groups: 6.16 ± 1.63 in controls, 6.41 ± 2.81 in primary infertility, and 6.14 ± 2.81 in secondary infertility, indicating no statistically significant variation ($p = 0.812$). T4 levels showed a slight numerical decline in both infertility groups (19.17 ± 8.09) compared to controls (22.41 ± 5.77), though this difference was not statistically significant ($p = 0.354$). Similarly, TSH levels were moderately elevated in the infertility groups (4.47 ± 1.59) relative to controls (3.11 ± 1.48), but this increase also did not reach statistical significance ($p = 0.69$). These findings highlight subtle differences in thyroid function between the groups,

with infertility cases exhibiting marginally lower T4 and higher TSH levels than controls.

DISCUSSION

Studies have repeatedly illustrated a significant correlation between thyroid dysfunction and menstrual disorders in infertile women. In this study, most of the healthy controls (88%) reported normal menstrual cycles, whereas oligomenorrhea and amenorrhea were significantly more common in primary (62.5%) and secondary (80%) infertility women, concurring with previous observations from previous research that infertile women with thyroid dysfunction are subject to greater frequencies of menstrual disorders.(12)

Biochemical tests showed no significant difference in mean T3 and T4 levels between the control and infertile groups, indicating that these hormones by themselves are not significant indicators of infertility in this population. However, TSH was elevated in both the primary and secondary infertility groups

relative to controls, showing a trend towards subclinical thyroid disease, although this difference was not statistically significant within this sample. These results confirm other studies where it is established that high TSH, specifically in the higher normal range, occurs more commonly in infertile women and correlates with menstrual dysfunction and anovulatory cycles.(29)

Sustaining evidence in the regional literature, including that of Pakistan and Bangladesh, indicates higher frequencies of hypothyroidism and menstrual abnormalities in infertile women than in euthyroid women. The routine assessment of serum TSH is recommended as an integral part of evaluating infertility, considering its sensitivity towards early thyroid dysfunction and its effect on reproductive physiology.(30)

The present study evaluated thyroid function and menstrual patterns in women experiencing primary and secondary infertility compared to a control group. Our findings revealed a significantly higher incidence of menstrual irregularities, particularly oligomenorrhea and amenorrhea, among infertile women than among controls. These observations are consistent with those of previous studies that have identified thyroid dysfunction as a contributing factor to abnormal menstrual cycles and ovulatory disturbances. Krassas *et. al.* (1) noted that hypothyroidism is frequently related to anovulation and menstrual irregularities such as oligomenorrhea and amenorrhea. In the present study, 25 of 40 women with primary infertility and 9 of 10 women with secondary infertility had irregular menstrual cycles, further lending support to the fact that deranged endocrine status compromise's reproductive function.(12)

In our control group, most (88%) of the women reported having regular menstrual cycles, compared with only 35% in the primary infertility group and 20% in the secondary infertility group. This trend replicates the study by Singh *et al.*, who found a similar trend, where 76% of fertile women had regular cycles compared to only 40% of infertile women. Such menstrual disruptions could represent minute thyroid dysfunctions, specifically subclinical hypothyroidism, that frequently are undiagnosed but do impair ovulatory function.(30)

Thyroid function was determined from serum measurements of T3, T4, and TSH, all of which are essential for maintaining reproductive physiology. Although the present review did not incorporate specific hormone levels, the sequence of menstrual disruption implies potential underlying thyroid defects. Poppe and Velkeniers (2) highlighted that slight abnormalities in thyroid hormone levels are sufficient to disturb the hypothalamic-pituitary-ovarian axis. In addition, Verma *et. al.*, (4) reported that women with unexplained infertility often had raised TSH levels, indicating the involvement of thyroid hormones in unexplained reproductive dysfunctions.(31)

The age distribution in our study revealed that the majority of participants in all groups were within the reproductive age range of 22–40 years. The major infertility group had a more dispersed distribution, whereas the secondary infertility group was bunched in the age range of 26–40 years. These findings agree with the age distribution of infertile women reported in previous studies. Sinha *et. al.*, (6) pointed out that hormonal imbalance leading to infertility occurs more frequently among women aged 25–35 years, at which time reproductive desire is maximum and subtle endocrine dysfunction starts becoming apparent (32). The observed pattern of menstrual disturbances also indicated potential metabolic involvement. Oligomenorrhea and amenorrhea are also known to be associated not only with thyroid dysfunction but also with high prolactin levels and polycystic ovarian morphology, which could either exist together in infertile cases or may be associated together. Krassas *et. al.*, and Hudson and Edwards both emphasized that thyroid dysfunction could indirectly influence other hormones, such as prolactin and androgens, further complicating menstruation. Our results justify the suggestion that females with infertility and cycle irregularity should be assessed with detailed endocrine work-up including TFTs.(33)

In summary, this study reaffirms the close link between thyroid function and reproductive health. Women with infertility, especially those with menstrual irregularities, should be screened for thyroid dysfunction as part of routine infertility evaluations. This evidence contributes to the increasing body of evidence that promotes early

detection and treatment of thyroid disorders to enhance fertility outcomes.

CONCLUSION

This study draws attention to the possible role of thyroid dysfunction, especially elevated TSH levels, in menstrual irregularities and infertility. Although T3 and T4 levels remained equal in all groups, the raised TSH levels in both the primary and secondary infertility groups indicate that even subclinical hypothyroidism can have some impact on reproductive health. These results highlight the role of thyroid function in fertility and lend credence to the call for thyroid screening in women with infertility, given that early detection would facilitate the identification of thyroid-related causes of menstrual irregularities and infertility.

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Conflict of interest: The authors declare no conflicts of interest.

Consent to participate: Informed consent was obtained from all participants included in the study, either directly or from their legal guardians.

Conclusion

Despite having a high emotional intelligence, ambulance workers struggle with considerable stress and fatigue as a result of their busy schedules and poor work-life balance. Although there are links between these parameters, more study is still required. It is still essential for their performance and general well-being to prioritize sleep, breaks, and healthier work habits. In order to support the well-being and maximize the performance of ambulance staff, this study highlights the obstacles they experience and highlights the necessity for interventions that promote healthy work practices and work-life balance.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

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