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ASSOCIATION BETWEEN THYROID DYSFUNCTION AND REPRODUCTIVE HORMONE PROFILES IN AN IRAQI POPULATION

HUBUNGAN ANTARA DISFUNGSI TIROID DAN PROFIL HORMON REPRODUKSI PADA POPULASI IRAK

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ABSTRAK

Disfungsi tiroid diketahui dapat menyebabkan gangguan endokrin dan metabolik, termasuk perubahan pada regulasi hormon reproduksi, namun bukti ilmiah yang bersifat spesifik populasi masih terbatas. Penelitian potong lintang ini bertujuan untuk mengevaluasi hubungan antara disfungsi tiroid dan profil hormon reproduksi pada populasi Irak. Sebanyak 210 partisipan dilibatkan dan dibagi ke dalam tiga kelompok, yaitu 70 pasien hipertiroid, 70 pasien hipotiroid, serta 70 individu sehat sebagai kelompok kontrol yang disesuaikan berdasarkan usia dan jenis kelamin, dengan melibatkan subjek laki-laki dan perempuan. Parameter yang dianalisis meliputi kadar serum TSH, FT3, FT4, testosteron, estrogen, luteinising hormone (LH), follicle-stimulating hormone (FSH), dan prolaktin, yang diukur menggunakan metode enzyme immunoassay. Hasil penelitian menunjukkan perbedaan bermakna pada kadar hormon tiroid yang mengonfirmasi klasifikasi klinis masing-masing kelompok. Pasien hipotiroid menunjukkan penurunan kadar FT3 dan FT4 disertai peningkatan TSH, sedangkan pasien hipertiroid menunjukkan peningkatan FT3 dan FT4 dengan supresi TSH. Selain itu, ditemukan perbedaan signifikan pada hormon steroid seks, di mana kadar testosteron dan estrogen lebih rendah pada pasien hipotiroid dibandingkan kelompok hipertiroid dan kontrol. Kadar prolaktin pada pasien hipotiroid lebih tinggi dibandingkan pasien hipertiroid, namun tidak melebihi kelompok kontrol. Tidak terdapat perbedaan signifikan pada kadar LH dan FSH antar kelompok. Pasien hipotiroid juga memiliki indeks massa tubuh yang lebih tinggi. Secara keseluruhan, temuan ini menegaskan bahwa disfungsi tiroid berpengaruh terhadap hormon reproduksi, khususnya hormon steroid seks dan prolaktin.

ABSTRACT

Thyroid dysfunction can disrupt endocrine and metabolic processes, including reproductive hormone regulation, yet population-specific data remain scarce. This cross-sectional study investigated the relationship between thyroid dysfunction and reproductive hormone profiles in an Iraqi population. The study involved 210 participants divided into three groups: 70 hyperthyroid patients, 70 hypothyroid patients, and 70 age- and sex-matched healthy controls, including both males and females. Serum levels of TSH, FT3, FT4, testosterone, oestrogen, LH, FSH, and prolactin were assessed using enzyme immunoassay methods. Distinct thyroid hormone patterns validated group classification. Hypothyroid patients exhibited decreased FT3 and FT4 levels with elevated TSH, whereas hyperthyroid patients showed increased FT3 and FT4 with suppressed TSH. Significant differences were also observed in sex steroid hormones. Testosterone and oestrogen levels were significantly lower in hypothyroid patients compared with hyperthyroid patients and controls. Prolactin concentrations were higher in hypothyroid patients than in hyperthyroid patients, though still lower than in healthy individuals. No significant differences were found in LH and FSH levels across groups.
Additionally, hypothyroid patients had a higher BMI than the other groups. Overall, the findings suggest that thyroid dysfunction, particularly

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thyrotoxicosis, affects sex steroid hormones and prolactin secretion, while gonadotropin levels remain relatively unchanged, emphasizing the role of thyroid hormones in reproductive endocrinology.

INTRODUSTION

The hypothalamus-pituitary-thyroid (HPT) axis helps regulate thyroid (thyroid hormone) function by regulating the secretion of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) from the pituitary gland, which then regulates the production of thyroxine (T4) and triiodothyronine (T3). Most T4 and T3 exist as bound forms in circulation, attached to transport proteins, primarily thyroxine-binding globulin, while the unbound (free) forms are the biologically active forms. Thyroid hormones play a role in regulating the metabolism of many tissues, as well as the growth and development of humans and other animals (including the maturation of reproductive systems and the ability of those systems to function). Therefore, if thyroid hormone levels are disrupted in the body, there can be many important systemic and endocrine (hormonal) problems associated with that disruption [Brent, G. A., 2012].

Hyperthyroid is usually identified by having both decreased serum TSH levels and elevated levels of free T3 and or free T4 whereas hypothyroid is characterized by an elevated TSH and decreased levels of both free T3 and free T4. Thyroid disease is viewed as one of the leading endocrine health issues and is generally thought of as one of the most common conditions diagnosed within an endocrinological setting, only behind diabetes [Carmona Ca, et all ,2018].. According to many researchers, variable and wide-ranging estimates of the prevalence of thyroid disorders are reported among the Middle Eastern and Arab populations and these differences in estimated prevalence can be attributed to variable definitions used in the respective studies, different levels of iodine exposure among the participating populations and variations in the make-up or structure of the populations from which the estimated prevalence is derived. Recent evidence from a large systematic review and meta-analysis demonstrate a continued high prevalence of thyroid dysfunction among adult populations in the Middle East, with further evidence of an increasing trend over the past 20 years, thus highlighting the need for continued population-based endocrine disease research in the region. Studies of the local population in Iraq have demonstrated evidence of a large burden associated with thyroid disease [Carosa, E et all, (2018) and (Gabrielson, A. T. et all, 2019]. , a lesser number of male populations affected compared with females and that middle-aged adults represent a disproportionate number of the positive diagnoses of thyroid disease, suggesting the need for further investigation on thyroid disorders within the Iraqi population [Hadgu, R., Worede, A., & Ambachew, S. 2024]..

Thyroid dysfunction is also related to changes in reproductive hormones such as testosterone, estrogen, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin, in addition to its effects on metabolism. However, many studies have not reported a consistent pattern of change in the type or amount of change across the studies published [Kargar, S., 2024]. Some of the currently available evidence from large and diverse populations indicates that there are differences in sex hormones and sex hormone-binding globulin (SHBG) concentrations based on thyroid status [Kjaergaard, A. D., 2021].. A number of the biological pathways that have been suggested for how thyroid hormones interact with reproductive tissues are through direct binding to nuclear receptors found within the testes and ovaries and other associated reproductive tissues [La Vignera, S., 2017] and [Selva, D. M., & Hammond, G. L., 2009].. Additionally, thyroid hormones are believed to influence the availability of steroid hormones via mechanisms such as changes in hepatocyte SHBG production. Specifically, DHN (the deiodinases) are hypothesized to regulate the transcriptional activity of HNF-4α and subsequently up-regulate SHBG production, therefore increasing the amount of sex hormones that are present in circulation [Silva, J. F., 2018]. Prolactin may also play a role through the synthesis and release of follicle-stimulating hormones and luteinizing hormones from the pituitary gland. There may be an indirect relationship between the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-thyroid axis [Zoori & Mousa. (2023). and Al-Ramahi et al. (nd]. The majority of the published data is derived from studies performed in

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populations other than those from the Middle East, and the lack of data on the relationship between thyroid hormones and reproductive hormones for both males and females in Iraq is still limited.

The purpose of this research study was to determine the levels of thyrotropin (thyroid stimulating hormone, or TSH), free 4-hydroxythyronine (T4) and free 3,3'-triiodo-L-thyronine (T3), found in subjects diagnosed with either hypothyroidism or hyperthyroidism, varies significantly when compared to healthy individuals and are associated with testosterone, estrogen, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin hormone levels found in the sex hormonal system and in the Iraqi population. In addition, larger population-based analyses suggest that there may be an underlying biological mechanism linking the thyroid function and sex hormones; thus, there is support for the hypothesis of a causal relationship between the two. The study aims to compare the serum concentrations of free T4, free T3, and TSH with the levels of testosterone, estrogen, prolactin, luteinizing hormone (LH), and follicle stimulating hormone (FSH), in subjects diagnosed with hypothyroidism and hyperthyroidism versus healthy individuals.

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RESEARCH METHODE

Study design and participants

Between January and June of 2023, a cross-sectional study took place at Basrah Teaching Hospital in Basrah, Iraq. 210 patients took part in this research. Participants were divided into two groups: hypothyroid patients (70) and hyperthyroid patients (70) diagnosed by their physicians through biochemical thyroid function tests. Men and women aged 18 to 65 from both groups were included. A matched control group of 70 healthy men and women were selected from the general population, and there were no previous records of thyroid disease or other endocrine disorders. The control subjects had an equal number of men and women as well as ages that corresponded to those of the patient subjects. Women who were pregnant or nursing; individuals with chronic liver disease or chronic kidney disease were not included in the study because these conditions can affect hormone metabolism. The Scientific and Ethical Committee of Basrah Teaching Hospital approved the study's design. All activities relating to the study were performed by the principles established in the Declaration of Helsinki regarding research involving humans [Yuchao Zang, et. all, 2021].

Blood sample collection and handling

Participants provided approximately 5 mL of venous blood following a 12 hour fast. Blood was drawn into Becton Dickinson (BD) Vacutainer SST™ tubes (USA), which were allowed to clot prior to being centrifuged at 3000 RPM for 10 minutes using the Hettich® Rotina 380 centrifuge (Andreas Hettich GmbH, Germany). After obtaining serum, it was transferred into sterile Eppendorf® tubes and stored at -20°C until analysis in the laboratory.

Hormonal measurements

Hormone levels in participants' serum were measured for thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total testosterone, total estrogen, luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin using colorimetric enzyme immunoassay methods. The Stat Fax® 4200 ELISA reader (Awareness Technology Inc., USA) was used to perform all assays and follow the manufacturer's guidelines. Hormone measurements occurred for both the patient and control groups.

Statistical analysis

Statistical analyses of data were carried out using IBM SPSS Statistics for Windows, (version 26.0). Continuous data are expressed as mean ± standard deviation (SD). One-way Analysis of Variances (ANOVA) was completed to compare the three groups of interest (hyperthyroidism, hypothyroidism and control). If needed, Tukey's post hoc test was performed to establish pair-wise comparisons between level of significance among the three groups. A p-value of less than 0.05 was judged to be statistically significant [Rolando Advíncula- Espino, 2025].

RESULT AND DISUSSION

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Result

A total of 210 individuals were analyzed, with 70 in each group, including hyperthyroid patients (n = 70), hypothyroid patients (n = 70), and healthy controls(n=70). An overview of the demographics and clinical characteristics of the cohort studied can be found in Table 1. There were no significant age or gender differences across the three groups (p=0.315, p=0.887 respectively). On the contrary, body mass index (BMI) differed significantly between the three groups (p<0.001). Patients with hypothyroidism demonstrated a higher BMI than both hyperthyroid patients and healthy controls. The disease duration was significantly higher in the hypothyroidism group compared to the hyperthyroid group (p = 0.003). Thyroid function parameters were significantly different between the three groups (see Table 2). There was a statistically significant difference between hyperthyroid, hypothyroid and control groups for serum TSH, (FT3), free triiodothyronine (FT3) and free thyroxine (FT4) levels. The patients with hypothyroidism had significantly elevated TSH concentrations and decreased concentrations of FT3 and FT4 when compared to the hyperthyroid and control groups. The hyperthyroid patients had significantly reduced TSH concentrations and increased concentrations of both FT3 and FT4 compared to the other groups.

By analyzing sex hormone concentrations, we found several significant differences among the groups studied based on the data presented in Table 2. The serum testosterone concentration for all three groups was significantly different (p = 0.002), with hyperthyroid patients having higher average testosterone concentrations than either the control or hypothyroid group, and the hypothyroid patients exhibiting the lowest average serum testosterone concentration. There was also a significant difference in serum estrogen concentration between all three groups (p = 0.008), with hyperthyroid individuals having the highest average serum estrogen concentration, while those in the hypothyroid population displayed the lowest means. The control population exhibited intermediate levels of serum estrogen. There was no significant difference between serum concentrations of luteinizing hormone or follicle stimulating hormone between any of the three groups (p = 0.15 and p = 0.22, respectively). Additionally, there was a large overall difference in serum prolactin levels among all study groups (p<0.001). Prolactin levels were significantly higher in the hypothyroid population than in both the hyperthyroid population and the control group, and hyperthyroid individuals had the lowest levels of prolactin.

The gender discrepancy in serum hormonal parameters found in these clinical study groups as shown in the Gender-Stratified Analysis for Hormonal Parameters (Table 3). Within each clinical study group, females had lower TSH concentrations than males were not different by gender analyses for any of the groups (hyperthyroid, hypothyroid, and control). However, within the hyperthyroid, hypothyroid, and control groups, males had much higher concentrations of testosterone than females (p < 0.001). In all three groups, males with hyperthyroidism had the highest concentrations of testosterone. In contrast, females with hypothyroidism displayed the lowest concentrations of testosterone. In contrast, serum estrogen concentrations were consistently lower in males compared to females, and statistically significant differences were present (p<0.001) across the three groups. Among females within the three clinical study groups, the highest level of serum estrogen concentration occurred in the hyperthyroid group, and the lowest occurred in the hypothyroid group, with the control group presenting estrogen concentrations that lie between these two extremes. The difference in serum prolactin concentration was consistently higher in females compared to males and reached statistical significance in the hypothyroid (p = 0.005) and control (p = 0.02) groups. There were no statistically significant gender differences in serum prolactin concentrations between male and female patients with hyperthyroidism.

Table 1: Demographic and clinical characteristics of the study participants by thyroid status

P-value	Control Group (N=70) Mean ± SD / n (%)	Hypothyroidism (N=70) Mean ± SD / n (%)	Hyperthyroidism (N=70) Mean ± SD / n (%)	Characteristic
0.315	46.1±9.8	48.7±12.1	45.2±10.5	Age (years)
0.887				Gender, n (%)
	35(50.0%)	36(51.4%)	34(48.6%)	Males
	35(50.0%)	34(48.6%)	36(51.4%)	Females
<0.001	23.5±2.9	27.5±4.2	24.8±3.1	Body Mass Index (kg/m2)
0.003	N/A	4.5±2.3	3.2±1.8	Disease Duration (years)

Table 2: Comparison of thyroid and reproductive hormone concentrations among control, hyperthyroid, and hypothyroid groups

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P-value (Overall Test)	Control (N=70) Mean ± SD	Hypothyroidism (N=70) Mean ± SD	Hyperthyroidism (N=70) Mean ± SD	Variable (Unit)
<0.001	2.1±0.8	15.2±3.5	0.05±0.02	TSH (mIU/L)
<0.001	4.2±0.7	2.5±0.6	9.8±1.5	FT3 (pmol/L)
<0.001	14.5±2.1	8.7±1.9	32.1±4.2	FT4 (pmol/L)
0.002	15.8±3.5	12.3±3.8	18.5±4.1	Testosterone (nmol/L)
0.008	135.0±22.0	120.0±20.0	155.0±25.0	Estrogen (pmol/L)
0.15	5.5±1.1	4.8±1.0	5.2±1.2	LH (IU/L)
0.22	7.3±1.6	6.5±1.5	7.1±1.8	FSH (IU/L)
<0.001	11.8±2.9	18.7±4.5	12.5±3.2	Prolactin (ug/L)

Table 3: Sex-stratified comparison of thyroid and reproductive hormone levels among control, hyperthyroid, and hypothyroid groups

P-value	Females (n=35) Mean ± SD	Males (n=35) Mean ± SD	Group	Variable (Unit)
0.15	0.06±0.02	0.04±0.01	Hyperthyroidism	TSH (mIU/L)
0.38	15.6±3.8	14.8±3.2	Hypothyroidism	
0.29	2.2±0.9	2.0±0.7	Control	
<0.001	3.9±1.1	23.1±3.5	Hyperthyroidism	Testosterone (nmol/L)
<0.001	2.8±0.9	18.7±3.0	Hypothyroidism	
<0.001	3.5±1.0	21.5±3.2	Control	
<0.001	220.0±30.0	90.0±15.0	Hyperthyroidism	Estrogen (pmol/L)
<0.001	165.0±25.0	75.0±12.0	Hypothyroidism	
<0.001	185.0±28.0	85.0±14.0	Control	
0.06	13.5±3.5	11.5±2.8	Hyperthyroidism	Prolactin (ug/L)
0.005	21.4±4.8	16.0±4.0	Hypothyroidism	
0.02	13.0±3.0	10.5±2.5	Control	

Discussion

This research analyzed how a person's thyroid dysfunction affects their sex hormones and reproductive hormones. We compared both male and female patients who were diagnosed with Hyperthyroidism, hypothyroidism, and healthy controls. It was found that thyroidal dysfunction on male and female patients produced significant differences in how much of an individual's sex hormones (estrogen, testosterone) and prolactin were in the bloodstream; this means that males and females with these dysfunctions had higher or lower than expected amounts of these hormones in their system, whereas Gonadotropins were not as impacted or changed from the controls; therefore, we have an indication that the main subject (Female and male) who did not have normal thyroid function had significantly higher or lower than expected hormone levels in the bloodstream. Thus far, this is consistent with what previous articles report, indicating that Thyroid Hormones affect the reproductive endocrine system due primarily to how they alter how the body's hormones are metabolized and interact with the hypothalamus and pituitary glands, but do not directly impact how much gonadotropins are released from the pituitary gland.

The study also demonstrated that on average, the hypothyroid patient group had a higher Body Mass Index (BMI) than both the hyperthyroid&controls. This finding is consistent with many other studies demonstrating strong associations between hypothyroidism and weight gain from having a lower than average Basal Metabolic Rate, abnormal levels of lipids in the body, and increased amounts of body fat due to a lack of thyroid hormones. Similar results were also reported in many countries, thereby further establishing the role of thyroid hormones in regulating metabolism and indirectly causing reproductive endocrine system disorders. Biochemical evaluation of thyroid function aided in grouping patients clinically into groups based on their biochemical results. Hypothyroid patients had high levels of TSH, low levels of FT3 & FT4; Hyperthyroid patients showed suppressed TSH/ In addition the hormone levels corresponded with established guidelines for diagnosing both conditions as well. Biochemical assessments of both conditions are also well established in clinical literature and through epidemiological

studies regarding thyroid diseases[Krassas, G. E., Poppe, K., & Glinoer, D., 2010] and [La Vignera, S., 2017]. Biochemical assessment demonstrated differences between hormonal levels among males based on their respective states of thyroid disease. For example, low testosterone concentrations were found within males suffering from hypothyroid conditions whereas males suffering from hyperthyroid conditions showed high concentrations of testosterone. The observations of elevated testosterone concentrations in association with hyperthyroid conditions were previously documented in relation to disruption of normal metabolism of androgens due to a malfunction of thyroid gland function [Zhang, Q. et all., 2017]. Hypothyroid patients were found to have lower testosterone levels as a result of steroidal hormones not being produced within the testicles as a result of impaired steroidogenesis, disrupting pathways utilized for metabolism and decreasing biochemical clearance rates for steroidal hormones [Krassas, G. E., Poppe, K., & Glinoer, D., 2010]. Hyperthyroid conditions are linked with the elevation of circulating testosterone through increased production of sex hormone binding globulin and through increase of the total amount of this hormone in the circulation; however, there are contradictory findings of decreased free testosterone from prior studies evaluating this particular type of thyroid dysfunction [La Vignera, S., 2017] and [Poppe, K., & Velkeniers, B., 2004]. Similar alterations of testosterone hormone patterns in male hyperthyroid patients after medical treatment with anti-thyroid medications have also been documented [Zhang, Q. et all., 2017].

The current research indicates a significant correlation between estrogen levels and thyroid status. Specifically, hypothyroid individuals were found to have significantly lower estrogen levels compared with normal or hyperthyroid individuals, who had significantly higher estrogen levels. These results are consistent with those of prior studies indicating that hypothyroidism leads to decreased ovarian activity, resulting in decreased estrogen levels and menstrual irregularities from impaired ovarian function. Conversely, hypothyroid individuals typically have elevated estrogen levels due to increased peripheral conversion of androgens to estrogens and altered liver metabolism of steroid hormones. Therefore, hormonal imbalances caused by changes in the thyroid and ovaries are responsible for the reproductive problems experienced by women suffering from thyroid disorders.

Hormonal imbalances caused by thyroid dysfunction may result in menstrual irregularities and decreased fertility. In contrast to the significant effect of sex steroid hormones on reproductive function, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) serum levels were not significantly altered between groups. This finding supports previous clinical observations that thyroid dysfunction does not consistently alter the secretion of LH and FSH from the pituitary in individuals without severe or long-term thyroid disease [Poppe, K., & Velkeniers, B., 2004]. These findings indicate that the majority of the reproductive hormone imbalance linked to thyroid disorders are due to peripheral changes in hormone production rather than primary problems with the hypothalamic-pituitary-gonadal (HPG) axis. In particular, hypo- and hyperprolactinemia are common findings in male and female hypothyroid patients when compared to hyperthyroid and control groups.

Hypothyroidism is associated with increased levels of prolactin due to increased levels of thyrotropin-releasing hormone, which stimulates the anterior pituitary to produce TSH and prolactin. High levels of prolactin can also worsen reproductive dysfunction by inhibiting production of gonadotropin-releasing hormone (GnRH) leading to more severe menstrual irregularities and difficulties with ovulation [Krassas, G. E., Poppe, K., & Glinoer, D., 2010]. On the other hand, it is possible that lower prolactin levels found in hyperthyroid patients may be due to modified regulation of the hypothalamus and/or increased levels of dopamine inhibition, which has been suggested in previous studies [La Vignera, S., 2017]. In comparing males to females (gender stratified) there were expected physiological differences, including higher levels of testosterone in males and increased levels of estrogen and prolactin in females for each group. Importantly, these hormonal differences between males and females persisted throughout the different thyroid states, but the degree of hormonal change between males and females was dependent upon thyroid status. The moderate hypo-functioning thyroid gland of women is shown through the very high prolactin hormone levels in women, indicating an increase in reproductive endocrine research on hypothyroidism in women.

The findings of the present study confirm earlier findings that thyroid dysfunction has a greater effect on reproductive function in women than do other endocrine gland disorders, especially during their reproductive years [La Vignera, S., 2017] and [Poppe, K., & Velkeniers, B., 2004]. The study's results indicate that thyroid dysfunction is correlated with significant decreases in sex hormones and prolactin levels, but gonadotropins drop relatively less than sex hormones and prolactin. The present study is consistent with earlier clinical findings and provides population-specific evidence from Iraq that is lacking in many published studies about thyroid and reproductive hormones in both genders. The findings of the present study indicate that longitudinal studies will be needed to further define the temporal nature of

reversal of thyroid function and reversal of reproductive hormone levels, as well as to investigate the impact of these reproductive hormones on fertility and health during pregnancy.

CONCLUSION

In conclusion, this study demonstrates that thyroid dysfunction is significantly associated with alterations in reproductive hormone profiles in both males and females, while gonadotropin secretion remains largely unaffected. Hypothyroidism was characterized by higher BMI, longer disease duration, elevated TSH, reduced FT3 and FT4, lower testosterone and estrogen levels, and significantly increased prolactin concentrations. In contrast, hyperthyroidism was associated with suppressed TSH, elevated FT3 and FT4, higher levels of sex steroid hormones, and lower prolactin levels. Gender-stratified analyses confirmed expected physiological differences between males and females; however, the magnitude of hormonal alterations varied according to thyroid status, with women—particularly those with hypothyroidism—exhibiting more pronounced reproductive endocrine disturbances. The absence of significant differences in LH and FSH levels across groups suggests that reproductive dysfunction related to thyroid disease is primarily driven by peripheral changes in sex steroid metabolism and prolactin regulation rather than direct disruption of the hypothalamic–pituitary–gonadal axis. Overall, these findings provide population-specific evidence from Iraq supporting the critical role of thyroid hormones in regulating reproductive endocrinology and metabolism. Comprehensive hormonal evaluation should therefore be considered essential in the clinical management of patients with thyroid disorders, and further longitudinal studies are warranted to clarify the reversibility and long-term reproductive implications of these hormonal changes.

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