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# Prevalence of Hyperprolactinemia in Overt and Subclinical Hypothyroidism at a Tertiary Center in Basra, Iraq

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## ABSTRACT

**Background:** Hyperprolactinemia is a common condition resulting from excessive prolactin secretion by pituitary lactotrophs. Both overt and subclinical hypothyroidism (ScH) contribute to its development.
**Objectives:** To assess the prevalence of hyperprolactinemia in patients with subclinical and overt hypothyroidism and explore its association with polycystic ovary syndrome (PCOS) and body mass index (BMI).
**Materials and methods:** This retrospective cross-sectional study included 917 women who underwent thyroid function and serum prolactin testing at Faiha Specialized Diabetes, Endocrine, and Metabolism Center in Basra between 2017 and 2023. Patients were categorized into euthyroid, ScH, and overt hypothyroidism based on thyroid-stimulating hormone (TSH) and free tetra-iodothyronine (FT4) levels. Hyperprolactinemia was defined as serum prolactin $\geq$ 20 ng/mL.
**Results:** The prevalence of hyperprolactinemia was 24.2%, with higher rates in ScH (36.1%) and overt hypothyroidism (35.9%) compared to the euthyroid group (21.7%). The median TSH levels were significantly higher in overt hypothyroidism than in ScH and euthyroid groups, while FT4 levels were significantly lower in overt hypothyroidism. PCOS was observed in 15.4% of participants, with no significant association with thyroid dysfunction. However, PCOS patients had significantly higher prolactin levels than non-PCOS patients. A moderate positive correlation was observed between TSH and prolactin levels in overt hypothyroidism, while no significant correlation was found in ScH.
**Conclusion:** Prolactin levels were significantly elevated in subclinical and overt hypothyroidism, emphasizing the need for prolactin assessment in these patients. PCOS patients exhibited higher prolactin levels. Future community-based assessments can strengthen these findings.
**Keywords:** Hyperprolactinemia; Hypothyroidism; Pituitary Function; Thyroid Dysfunction; Polycystic Ovary Syndrome

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## INTRODUCTION

Hyperprolactinemia is the most prevalent endocrine pathology of the hypothalamic-pituitary axis. Clinical features include oligoamenorrhea, decreased libido, infertility, galactorrhea, in addition to headaches and visual changes from the mass effect [1].

The common causes of hyperprolactinemia include pituitary tumours, hypothyroidism, stress and drug induced. It is relatively more common in females than males [2].

Prolactin (PRL) is regulated by two hypothalamic hormones transported through the hypothalamic-pituitary circulation. The primary regulation is inhibitory, mediated by dopamine, which suppresses PRL release. In contrast, thyrotropin-releasing hormone (TRH) acts as a stimulatory signal. In hypothyroid patients, elevated PRL levels result from a compensatory rise in hypothalamic TRH secretion due to reduced thyroxine levels [3]. In 1988, for the first time, an

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increase of serum PRL was reported in a woman with carpal tunnel syndrome and subclinical hypothyroidism (ScH) [2].

Hypothyroidism is also a common condition, affecting approximately 5% of the general population, with an additional 5% remaining undiagnosed. A survey conducted in Iraq reported a prevalence of hypothyroidism in 4.48% of the studied population [4]. ScH is often asymptomatic, leading to underrecognition in clinical settings [5]. As a result, associated conditions like hyperprolactinemia could be missed and remain undetected.

Hyperprolactinemia in overt hypothyroidism has been reported in up to 40% of cases [2]. However, a limited number of studies, primarily in the Southern regions of Iraq, have documented its prevalence and clinical significance in ScH. Additionally, polycystic ovary syndrome (PCOS), a common hormonal condition in women of reproductive age, has similar symptoms to hyperprolactinemia, such as irregular periods and difficulty getting pregnant. Both hypothyroidism and hyperprolactinemia have also been linked to increased body mass index (BMI) [6, 7].

This retrospective study aims to estimate the prevalence of hyperprolactinemia in patients with overt and ScH and to investigate its association with PCOS and BMI.

## MATERIALS AND METHODS

This is a retrospective cross-sectional study conducted at Faiha Specialized Diabetes, Endocrine, and Metabolism Center in Basra City, Iraq. All patients evaluated with thyroid function tests and PRL levels were considered for the study. The data was extracted from the laboratory database during the period from February 2017 to January 2023, and patients were subjected to the inclusion and exclusion criteria.

*Inclusion criteria*: Females aged 18 years or older with available clinical data, including age, sex, weight, height, and documented clinical notes regarding diagnoses and other comorbidities.

Exclusion criteria: include individuals younger than 18 years, males, pregnant or lactating women, cases with incomplete data entry, patients with known or undiagnosed hyperthyroidism, known cases of prolactinoma, drug-induced hyperprolactinemia, and those with comorbid conditions such as chronic liver disease or chronic kidney disease. All these details were documented by the specialist in the clinical notes for each patient from the database.

BMI was calculated for each patient using the standard formula: BMI = weight (kg) / height$^2$ (m$^2$). Based on the calculated BMI values, patients were classified into four categories according to the World Health Organization (WHO) classification: Underweight (BMI $<$ 18.50), normal weight (BMI 18.50–24.99), overweight (BMI 25.00–29.99), and obese (BMI $\geq$ 30.00) [8].

Participants were classified into three categories according to their thyroid function profile: Normal (euthyroid), ScH, and overt hypothyroidism.

The reference range of thyroid-stimulating hormone (TSH) and free tetra-iodothyronine (FT4) were 0.5-4.0 mIU/L and 0.8-1.8 ng/dL, respectively. Hyperprolactinemia was defined as serum PRL level $\geq$ 20 ng/mL using the American Board of Internal Medicine (ABIM) laboratory test reference ranges published in January 2024 [9].

Subclinical hypothyrodism was defined as patients having normal FT4 levels with TSH levels above the reference range, while overt hypothyroidism was defined as having TSH levels above 10 mIU/L with low FT4 levels [5].

All procedures in this study were conducted in accordance with the ethical standards of the institutional and national research committees and the Declaration of Helsinki (1964), as revised in 2013. Ethical approval was granted from the Ministry of Higher Education, University of Basrah, College of Medicine, and Research Ethics Committee consent was obtained (Document No.5, Dated 21-03-2023). Informed consent from the participants was waived owing to the retrospective nature of the study.

The data were coded and analyzed using the statistical package for the social sciences (SPSS) version 26, developed by IBM Corporation, Armonk, New York, USA. Numeric variables were described using the mean, median, interquartile range, and standard deviation, depending on the normality of the data distribution. The normality of distribution was tested using the Shapiro-Wilk test. Categorical data were formulated as frequencies and percentages. The Chi-square test was used to test the significance of the association between categorical variables. Mann-Whitney U test and Kruskal-Wallis one-way ANOVA were employed to compare differences between two groups or more for non-normally distributed data. A P-value of $< 0.05$ was the criterion of statistical significance.

## RESULTS

A total of 1733 patients who underwent thyroid function evaluation and serum PRL measurement at Faiha Specialized Diabetes, Endocrine, and Metabolism Center were considered for the study. Of these, 917 women met the inclusion and exclusion criteria and were enrolled in the study, as demonstrated in Figure 1.

The mean age of the participants was 29.86 ± 9.21 years. The mean BMI of the participants was 31.44 ± 8.22. Nearly half of the study sample (n= 473) fell into the obese category.

Hyperprolactinemia was prevalent in 24.2% (n = 222) of the participants. PCOS was seen in 15.4% (n = 141), as shown in Table 1.

The distribution of thyroid function groups is illustrated in Table 2. ScH was prevalent in 13% (n = 119) of the participants, and only 4.3% (n = 30) had overt hypothyroidism.

A comparison of the clinical and laboratory characteristics across thyroid function study groups was conducted, and it revealed that age distribution was not statistically different between the three groups (P-value = 0.077). The median BMI was higher in the overt hypothyroidism group than in

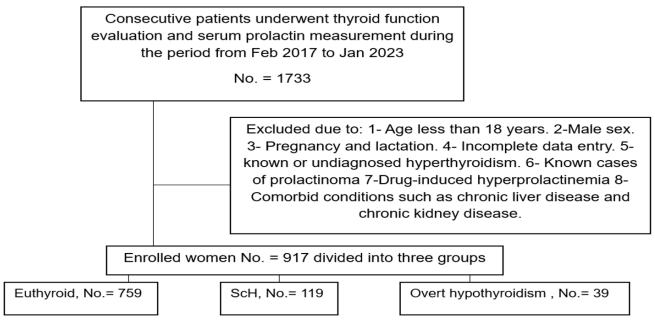


**Figure** 1. The study flowchart. No.= Number, ScH= Subclinical hypothyroidism.


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**Table** 1. The sociodemographic and clinical characteristics of the study population. PCOS = Polycystic ovary syndrome.

| Variables | | Mean ± SD | Median (IQR) | Number | % |
|---|---|---|---|---|---|
| Age (years) | | 29.86 ± 9.21 | 28.00 (13) | | |
| Weight (kg) | | 79.03 ± 21.18 | 77.00 (27) | | |
| Height (cm) | | 158.37 ± 6.76 | 159.00 (7) | | |
| BMI | | 31.44 ± 8.22 | 30.12 (9.94) | | |
| | Underweight | | | 30 | 3.3 |
| | Normal | | | 161 | 17.6 |
| | Overweight | | | 253 | 27.6 |
| | Obese | | | 473 | 51.5 |
| Hyperprolactinemia | | | | | |
| | Yes | | | 222 | 24.2 |
| | No | | | 695 | 75.8 |
| PCOS | | | | | |
| | Present | | | 141 | 15.4 |
| | Absent | | | 776 | 84.6 |
| Total | | | | 917 | 100.0 |

**Table** 2. Classification of the study population according to thyroid function test results.

| Thyroid Function | Number | Percentage (%) |
|---|---|---|
| Euthyroid | 759 | 82.8 |
| Subclinical hypothyroidism | 119 | 13.0 |
| Overt hypothyroidism | 39 | 4.3 |
| Total | 917 | 100.0 |

the euthyroid and ScH (P-value = 0.044). However, the pairwise post hoc comparisons did not show significant differences in BMI for the three groups after adjusting for multiple comparisons. The proportion of PCOS was not significantly different across the three groups (P-value = 0.89). There was a progressively higher median level of TSH in the overt hypothyroidism group than in the ScH and euthyroid groups. Post hoc confirms that significant differences in TSH were present between overt hypothyroidism and ScH on one hand and the euthyroid group on the other hand (adjusted P-value = 0.0001). Contrarily, median FT4 levels were significantly lower in the overt hypothyroid group compared to the euthyroid and ScH groups, which was confirmed with post hoc comparison (adjusted P-value = 0.002). The serum PRL levels were significantly different between the three groups. The post hoc test indicated that the difference is statistically significant between the euthyroid and ScH groups (P-value = 0.0001). A significantly (P-value = 0.001) higher proportion of high PRL levels was seen among the ScH (36.1%) and overt hypothyroid (35.9%) groups compared to the euthyroid group (21.7%) as illustrated in Table 3.

The BMI, serum TSH, serum FT4, and serum PRL levels were further analyzed concerning the presence or absence of PCOS. There was a statistically significant difference in BMI between the two groups. Patients with PCOS tend to have higher BMI compared to those without PCOS (P-value = 0.033). In the same way, the serum PRL levels are usually much higher in patients with PCOS than in those without PCOS (P-value = 0.009), as shown in Table 4.

The correlation between PRL and TSH levels among patients with ScH and overt hypothyroidism was demonstrated in Table 5. The correlation between TSH and PRL in ScH was very weak and not statistically significant (r = 0.009, P-value = 0.920). However, overt hypothyroidism showed a moderate positive correlation between TSH and PRL levels which was statistically significant (r = 0.391, P-value = 0.014).

## DISCUSSION

The association of primary hypothyroidism and hyperprolactinemia was first reported in 1971 by Edwards et al., who confirmed the presence of hyperprolactinemia in a female patient presenting with galactorrhea with primary hypothyroidism [10]. It is estimated that in every seven women with hyperprolactinemia, one would have hypothyroidism [3]. This study's main strength lies in its large sample size compared to other earlier studies, particularity within a Middle Eastern population. Furthermore, our study adds to the existing literature by investigating PRL levels in women with PCOS which represent a controversial area in research. The study also points towards the importance of considering PRL screening in both overt hypothyroid patients and ScH, who may otherwise go undetected.

In the present study, the prevalence of ScH and overt hypothyroidism was 13% and 4.3%, respectively. These figures are in close approximation with a cross-sectional study in India in which 16.6% of the patients had ScH and 4% of them were found to have overt hypothyroidism [2]. The similarity in prevalence rates among different populations suggests a similar burden of thyroid dysfunction in women undergoing thyroid function evaluation. The relatively high prevalence of ScH is of particular importance, as it often remains asymptomatic. When symptoms do occur, they are typically vague and can mimic those of overt hypothyroidism, including tiredness, reduced energy, weight gain, sensitivity to cold, and constipation [11]. These findings underscore the significance of evaluating thyroid function in high-risk populations, especially among women of childbearing age.

In our study, hyperprolactinemia was found in approximately a quarter of the participants. Hyperprolactinemia was seen in 36.1% of those with ScH and 35.9% of overt hypothyroidism patients, significantly higher compared to the euthyroid group. Our findings are notably higher than Bahar et

**Table** 3. The clinical and laboratory characteristics across thyroid function groups[¶].

| Variable | | Euthyroid | ScH | Overt Hypothyroid | P-value‡ | Adjusted P-value† |
|---|---|---|---|---|---|---|
| Age | | 28.00 (12) | 27.00 (16) | 31.00 (10) | 0.077** | |
| BMI | | 29.97 (9.64) | 30.48 (12.26) | 31.76 (34.04) | 0.044** | P-values > 0.05§ Euthyroid = ScH = Overt |
| | Underweight | 27 (3.6%) | 3 (2.5%) | 0 (0.0%) | 0.08* | |
| | Normal | 130 (17.1%) | 25 (21.0%) | 6 (15.4%) | | |
| | Overweight | 223 (29.4%) | 24 (20.2%) | 6 (15.4%) | | |
| | Obese | 379 (49.9%) | 67 (56.3%) | 27 (69.2%) | | |
| PCOS | | | | | | |
| | Present | 115 (15.2%) | 20 (16.8%) | 6 (15.4%) | 0.89* | |
| | Absent | 644 (84.8%) | 99 (83.2%) | 33 (84.6%) | | |
| TSH | | 1.90 (1.40) | 5.30 (1.68) | 19.70 (32.10) | 0.0001** | P-value = 0.000 Overt= ScH > Euthyroid |
| FT4 | | 1.20 (0.23) | 1.10 (0.28) | 0.90 (0.60) | 0.0001** | P-value = 0.002 Overt < ScH < Euthyroid |
| PRL | | 15.70 (12.90) | 21.00 (18.31) | 19.70 (16.02) | 0.0001** | P-value = 0.000 Overt = ScH > Euthyroid |
| | Normal | 594 (78.3%) | 76 (63.9%) | 25 (64.1%) | 0.001* | |
| | Elevated | 165 (21.7%) | 43 (36.1) | 14 (35.9%) | | |
| Total | | 759 (100.0%) | 119 (100.0%) | 39 (100.0%) | | |

¶ BMI = Body mass index, PCOS = Polycystic ovary syndrome, TSH = Thyroid stimulating hormone, FT4 = Free tetra-iodothyronine, PRL = Prolactin, ScH = Subclinical hypothyroidism, * Chi-square test, ** Kruskal–Wallis 1-way ANOVA, ‡ Unadjusted p-value, † Adjusted P-value by Bonferroni Correction, § Exact Adjusted P-values: 0.523 (Normal–ScH), 0.083 (Normal–Overt), and 0.654 (ScH–Overt). Quantitative data are expressed as Median (IQR), Categorical data are expressed as No. (%).

**Table** 4. Comparison of BMI, TSH, FT4, and PRL levels according to the presence of PCOS[*].

| | BMI | | | |
|---|---|---|---|---|
| PCOS | No. | Mean Rank | Mann-Whitney U | P-value |
| Yes | 141 | 502.67 | 48551 | 0.033 |
| No | 776 | 451.07 | | |
| | TSH | | | |
| Yes | 141 | 482.09 | 51453 | 0.261 |
| No | 776 | 454.81 | | |
| | FT4 | | | |
| Yes | 141 | 459.39 | 54652 | 0.985 |
| No | 776 | 458.93 | | |
| | PRL | | | |
| Yes | 141 | 512.33 | 47188 | 0.009 |
| No | 776 | 449.31 | | |

* BMI = Body mass index, PCOS = Polycystic ovary syndrome, TSH = Thyroid stimulating hormone, FT4 = Free tetra-iodothyronine, PRL = Prolactin.

al. [12] which revealed a prevalence of hyperprolactinemia of 22% in women with ScH. Likewise, a study by Meier et al., on sixty-six female patients with ScH revealed a prevalence of hyperprolactinemia of 19% [13]. Additionally, Meier et al. reported that hyperprolactinemia responded to treatment with Levothyroxine, an aspect not explored in our study. These variations could be attributed to differences in study design, sample size, population characteristics, diagnostic criteria, and laboratory methods.

This study found that the median PRL level was not significantly different between the ScH and overt hypothyroid groups after adjustment for multiple comparisons, with a comparable prevalence of hyperprolactinemia in both groups (36.1% vs. 35.9%). Contrarily, Hekimsoy et al. [14] reported a comparable prevalence of hyperprolactinemia in overt hypothyroidism (36%); however, a significantly lower rate was seen in ScH (22%). A study by Goel et al. [15] also found a higher prevalence of hyperprolactinemia among overt hypothyroidism in comparison with ScH. Both studies included male patients and were conducted on only newly diagnosed hypothyroid cases. There are several mechanisms behind the elevated PRL in hypothyroidism, one is that the high levels of TRH that occur in primary hypothyroidism cause thyrotroph and lactotroph hyperplasia, potentially leading to hyperpro-


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**Table** 5. The correlation of PRL and TSH levels in patients with ScH and overt hypothyroidism*.

| Thyroid Function | Spearman Correlation Coefficient (r) | P-value |
|---|---|---|
| Subclinical Hypothyroidism | 0.009 | 0.920 |
| Overt Hypothyroidism | 0.391 | 0.014 |

* TSH = Thyroid stimulating hormone, FT4 = Free tetra-iodothyronine, PRL = Prolactin, ScH = Subclinical hypothyroidism.

lactinemia [16]. Second, decreased PRL clearance [16] and third, reduced sensitivity to the inhibitory action of dopamine and dopamine agonists, which stimulate PRL production [15].

In a study from India in 2019 [17], the mean BMI was significantly higher in over hypothyroidism compared to ScH (31.89 ± 6.79 vs. 31.25 ± 6.60). Our study found that the median BMI progressively increased from the euthyroid to subclinical to overt hypothyroidism groups, but post hoc comparisons showed no significant differences after adjusting for multiple comparisons. Hypothyroidism is associated with reduced thermogenesis, a higher BMI, and a lower metabolic rate. An increased prevalence of ScH has also been observed in obese individuals. Even among euthyroid individuals, obesity is linked to alterations in thyroid parameters. Several studies have shown a negative correlation between FT4 and BMI, as well as a positive correlation between TSH and BMI [18, 19].

Our study also found no association between thyroid function and PCOS. Likewise, in a study from the Netherlands, women with PCOS were not different from controls concerning thyroid dysfunction prevalence [20]. In contrast, a large study in China found that PCOS was linked to hyperthyroidism [21]. Our study could not analyze the association with hyperthyroidism cases because they were excluded.

In our study, women with PCOS had significantly higher PRL levels. Although several hypotheses attempt to explain the link between hyperprolactinemia and PCOS, controversies persist. Some evidence suggests that when a thorough etiological investigation of hyperprolactinemia is conducted, no direct association with PCOS is found [22]. In this context, Ham et al. [20], Kyritsi et al. [23], and Konrad et al. [24] found no association between PCOS and elevated PRL. However, measuring the serum level of PRL in PCOS is recommended, and pituitary magnetic resonance imaging (MRI) should be considered to exclude prolactinoma [23].

In a study by Koner et al. on newly diagnosed female patients with hypothyroidism, the mean TSH was significantly higher in overt hypothyroidism (23.84 $\mu$IU/ml) than ScH (9.83 $\mu$IU/ml) (P-value $<$ 0.0001). Additionally, the mean FT4 was significantly lower in overt hypothyroidism (0.61 *vs.* 1.35 ng/dl, P-value = 0.002) [17]. This aligns with our study results which revealed a progressively higher median level of TSH and lower FT4 in the overt hypothyroidism group than in ScH and euthyroid groups.

Our results demonstrated positive correlations between TSH and PRL levels among patients with ScH and overt hypothyroidism, which was significant for those with overt hypothyroidism (r = 0.391, P-value = 0.014). A similar correlation was also seen in Sirohi et al. and Hekimsoy et al. studies, which also reported higher rates of infertility [14, 25]. Moreover, a meta-analysis of 11 articles conducted in 2024 revealed a positive correlation between serum PRL and TSH in infertile women was found which was explained by the link of the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-ovarian axis [26]. The infertility was not specifically addressed in our study.

The limitations of this study include the inability to establish a causal relationship between hypothyroidism and hyperprolactinemia due to the cross-sectional study design. The study was subjected to information bias due to its reliance on laboratory databases. We could not exclude all cases of prolactinoma because pituitary imaging was either not performed or not documented. Furthermore, the limited generalizability of the results since it was conducted in a single center.

## CONCLUSION

This study found a significant association between hypothyroid states and elevated PRL levels. Hyperprolactinemia was markedly more prevalent in women with ScH and overt hypothyroidism compared to euthyroid individuals. This supports the need for assessment of PRL in women with ScH and overt hypothyroidism. Although BMI was higher in the overt hypothyroidism group, it did not show a statistically significant difference after adjustment. Additionally, PCOS patients showed significantly higher PRL levels, suggesting the need for routine PRL screening in this group. We suggest further studies regarding the effect of levothyroxine replacement and conducting community-based studies to investigate these associations with further depth.

## ETHICAL DECLARATIONS

### Acknowledgments

None.

### Ethics Approval and Consent to Participate

Ethical approval was granted from the Ministry of Higher Education, University of Basrah, College of Medicine. (Document number 5, Dated 21-03-2023). Informed consent from the participants was waived owing to the retrospective nature of the study.

### Consent for Publication

Not applicable. This manuscript does not contain any person's data in any form (including individual details, images, or videos).

### Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Competing Interests

The authors declare that there is no conflict of interest.

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**Authors' Contributions**

Al-Rubaye AA: Conceptualization, study design, writing original draft preparation, writing review and editing. Alibrahim NT: Conceptualization, data collection, drafting the article and reviewing. Both authors read and approved the final version of the manuscript.

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