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ORIGINAL ARTICLE

Hormonal interplay in hyperprolactinemia: Insights from a large-scale study of reproductive-age patients

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ABSTRACT

Objective: This study examined serum prolactin and reproductive hormone levels in women with elevated prolactin levels, with a particular focus on fertility status. The objective was to understand how prolactin affects reproductive hormones in infertile women, aiming to improve diagnostic and therapeutic strategies.

Material and Methods: The study involved 847 women aged 18–46 years who visited gynecology outpatient clinics between January and October 2019. Participants with prolactin levels ≥26 µg/L underwent hormone testing on the second or third day of menstruation. Patients were categorized based on fertility status and prolactin levels, specifically into groups of 26–100 µg/L and >100 µg/L. Demographics, symptoms, medical history, and hormone profiles were analyzed using NCSS 2007 software, employing descriptive methods, the chi-squared test, and Spearman's correlation.

Results: A statistically significant yet very weak negative correlation was identified between prolactin and estradiol levels in patients with moderate hyperprolactinemia (26–100 µg/L), as well as in both infertile and non-infertile subgroups. No significant associations were found between prolactin and gonadotropins (FSH=follicle-stimulating hormone, LH=luteinizing hormone) or progesterone, regardless of prolactin level or fertility status. In patients with highly elevated prolactin levels (≥100 µg/L), no statistically significant correlation was observed between prolactin levels and any measured reproductive hormone levels.

Conclusion: This cross-sectional study provides insights into the hormonal interplay in hyperprolactinemia, showing that serum prolactin levels are weakly correlated with estradiol levels and are not significantly associated with gonadotropin levels in clinical settings. These findings suggest that prolactin may impair reproductive function through indirect mechanisms not captured by static hormone measurements. Future research should incorporate longitudinal designs and clinical outcomes to further elucidate the relationship between prolactin and reproductive function.

Keywords: Estradiol, gonadotropins, hyperprolactinemia, infertility, reproductive hormones.

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INTRODUCTION

Hyperprolactinemia, the most prevalent endocrine disorder affecting the hypothalamic-pituitary axis, is a significant concern in gynecological endocrinology owing to its association with hypogonadism and infertility.[1] Pathological hyperprolactinemia is characterized by elevated serum prolactin (PRL) levels resulting from excessive prolactin secretion, excluding physiological causes. The diagnosis is confirmed when serum PRL levels, measured on two separate occasions, exceed the normal range established by the laboratory, typically with an upper limit of 20 ng/mL (20 µg/L SI units) or 400–500 mU/L.[2] The prevalence is 5% among individuals attending family planning clinics, 9% among those with primary amenorrhea, and 17% among women diagnosed with polycystic ovary syndrome.[3]

Prolactin is known to adversely affect the reproductive axis by reducing gonadotropin-releasing hormone (GnRH) secretion.[4] Animal studies have shown that elevated PRL levels lead to a decrease in both the amplitude and frequency of luteinizing hormone (LH) pulsations.[5,6] However, despite reports indicating that most GnRH-secreting neuronal cells lack PRL receptors,[7] it has been discovered that GnRH release is not directly influenced by PRL levels. Instead, it is indirectly regulated by kisspeptin, a regulatory neurocell type.[8–10] An increase in the frequency of GnRH pulsation is correlated with a predominance of LH secretion, whereas a decrease in pulsation results in hypothalamic amenorrhea characterized by dominant follicle-stimulating hormone (FSH) gonadotropin secretion.[11] Studies have indicated that causes of hyperprolactinemia that do not result in structural changes in pituitary gonadotroph cells, such as drugs or functional causes, lead to dominant FSH secretion.[11,12] In contrast, organic causes such as adenomas directly reduce both FSH and LH levels. These findings suggest that PRL levels could serve as a predictor of changes in gonadotropin levels, aiding in determining both the etiology and severity of symptoms such as amenorrhea and infertility.[12]

Although hyperprolactinemia is a well-recognized cause of reproductive dysfunction, the relationship between elevated prolactin levels and other reproductive hormones—particularly gonadotropins, estradiol, and progesterone—remains unclear. Existing data are limited and often inconsistent, largely owing to the complex hormonal interplay and variability in the underlying causes of hyperprolactinemia.[12,13] Most studies lack stratification by fertility status and often do not explore hormonal correlations in a clinically meaningful manner. Understanding how prolactin interacts with key reproductive hormones in infertile individuals is essential for improving diagnostic accuracy and treatment planning. This large-scale study aimed to address this gap by examining the correlation between serum prolactin and gonadotropin levels (FSH and LH), as well as estradiol, progesterone, and thyroid-stimulating hormone (TSH) levels, in patients with hyperprolactinemia, with a focus on infertility.

MATERIAL AND METHODS

The study included women who attended the gynecology outpatient clinics at Zeynep Kamil Women and Children's Diseases Training and Research Hospital from January to October 2019. These participants sought consultation for infertility, characterized by the inability to conceive after 12 months of regular intercourse, or for other conditions related to menstrual disorders such as oligomenorrhea or amenorrhea. The participants underwent serum hormonal profile tests on the second or third day of their menstrual cycle. Patients with serum prolactin levels ≥26 µg/L, indicative of hyperprolactinemia, were included in this study. Demographic data, symptoms and findings, history of chronic diseases, and hormone profiles (FSH, LH, estradiol, progesterone, and TSH) of the patients were reviewed and recorded through the hospital data system following the Zeynep Kamil Women and Children's Diseases Training and Research Hospital's ethics committee approval (18.09.2019/86). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients with chronic illnesses, a history of systemic drug use, or treatments that could affect their hormone profiles were excluded. The remaining patients were categorized into two groups: infertile and other diagnoses; the latter included menstrual cycle-related disorders such as oligomenorrhea and amenorrhea. They were further divided based on prolactin levels into those with slightly elevated levels (26–100 µg/L) and those with highly elevated levels (>100 µg/L). The results were statistically analyzed to explore the contribution of endocrine profile changes to hyperprolactinemia, to correlate PRL levels with LH, FSH, estradiol, and progesterone levels, and to identify their relationship with infertility. The patient selection process and exclusion criteria are summarized in a flow chart (Fig. 1).

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analyses. To evaluate the study data, descriptive statistical methods such as mean, standard deviation, frequency, percentage, minimum, and maximum were utilized. The normality of the distribution of quantitative data was assessed using the Shapiro–Wilk test and graphical analyses. Pearson's chi-square test was applied for comparing qualitative data, while Spearman correlation analysis was conducted to examine relationships between quantitative variables. Statistical significance was set at $p<0.05$.

RESULTS

The initial cohort comprised 1,153 patients. Of these, 36 pregnant women (due to physiological hyperprolactinemia), 67 patients with a diagnosis of endometriosis (owing to the potential impact on reproductive hormone balance), and 203 patients with incomplete hormonal profiles (lacking data on parameters other than prolactin) were excluded. The final study population included 847 patients aged 18–46 years, with a mean age of 30.9±6.6 years. Serum prolactin levels in this group ranged from 26.13 to 258.14 µg/L, with a mean of 43.07±23.25 µg/L. Comprehensive hormonal measurements, including estradiol (E2), progesterone, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the LH/FSH ratio, are presented in Table 1. Notably, 75.3% (n=638) of the patients were diagnosed with infertility.

In patients with moderately elevated prolactin levels (26–100 µg/L), a statistically significant but very weak negative correlation (0.084) was observed between prolactin and E2 levels ($r=-0.084$, $p=0.018$). A statistically significant positive correlation at a very

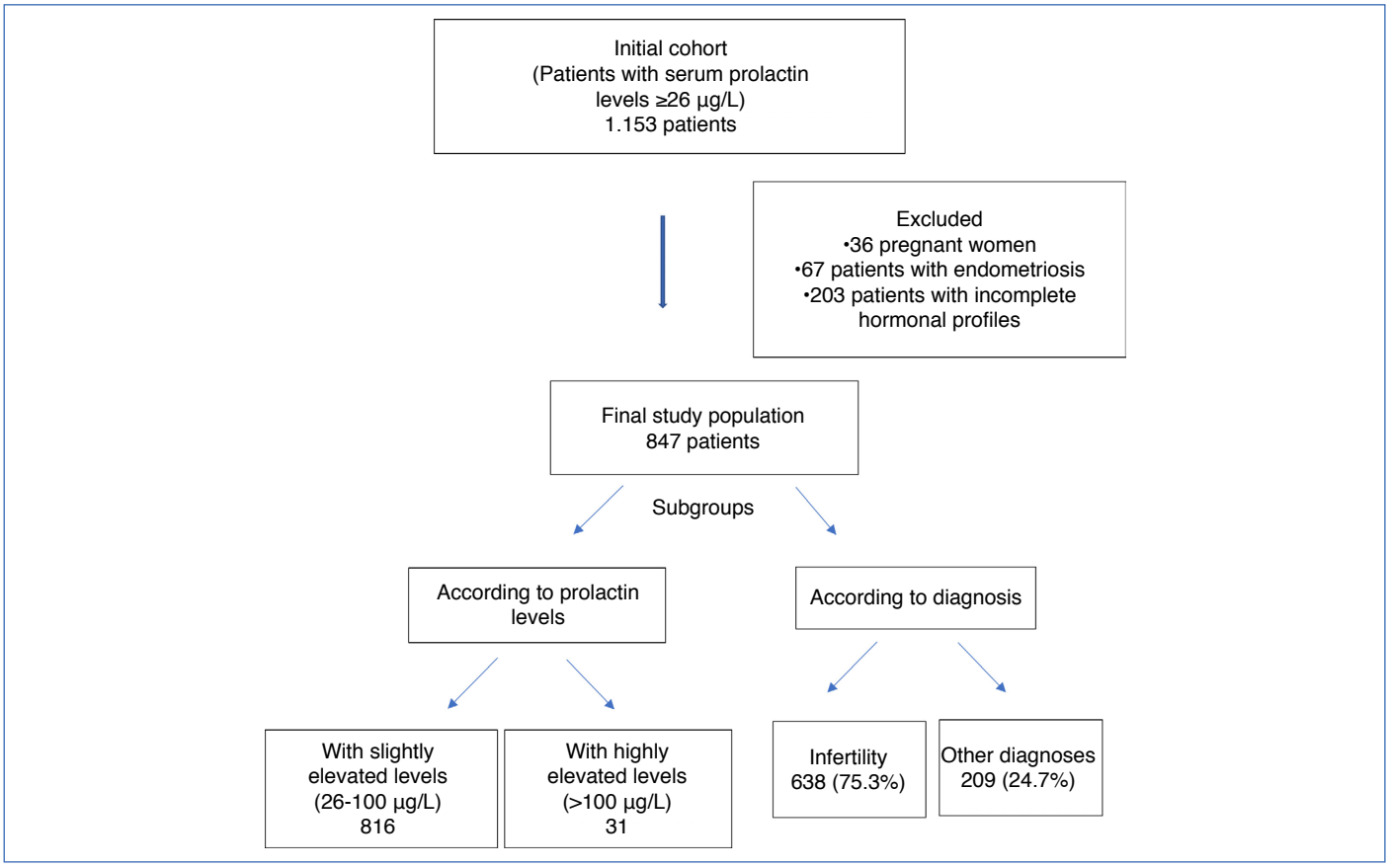

Figure 1: Flow chart of patient selection and exclusion criteria.

weak level (0.074) was found between prolactin and progesterone levels (r=0.074, p=0.042). No statistically significant correlation was found between prolactin levels and TSH, LH, FSH, or LH/FSH levels (p>0.05) (Table 2).

In patients with highly elevated prolactin levels (≥100 µg/L), no statistically significant correlation was observed between prolactin levels and E2, progesterone, TSH, LH, FSH, or the LH/FSH ratio (p>0.05) (Table 2).

In patients diagnosed with infertility, a very weak yet statistically significant negative correlation was observed between prolactin and E2 levels, with a correlation coefficient of -0.100 and a p-value of 0.012. However, no statistically significant correlations were identified between prolactin levels and progesterone, TSH, LH, FSH, or the LH/FSH ratio (p>0.05) (Table 3).

In patients with other diagnoses, a very weak yet statistically significant negative correlation of -0.166 was observed between prolactin and E2 levels (r=-0.166, p=0.021). However, no statistically significant relationships were identified between prolactin levels and progesterone, TSH, LH, FSH, or the LH/FSH ratio (p>0.05) (Table 3).

DISCUSSION

This large-scale cross-sectional study explored the correlation between serum prolactin levels and reproductive hormones (FSH, LH, estradiol, progesterone, and TSH) in women with hyperprolactinemia stratified by both fertility status and degree of prolactin elevation. Our findings revealed a statistically significant yet very weak negative correlation between prolactin and estradiol levels, particularly among patients with moderate hyperprolactinemia, as well as within both the infertility and other diagnoses subgroups. Notably, no significant associations were found between prolactin and gonadotropins or progesterone, irrespective of prolactin levels or fertility status.

These findings are consistent with previous evidence suggesting that prolactin suppresses the hypothalamic–pituitary–gonadal axis primarily by reducing GnRH pulsatility rather than by directly acting on gonadotrophs, given that GnRH neurons largely lack prolactin receptors. Instead, this suppression is likely mediated by kisspeptin inhibition, as demonstrated in both animal and human models.[14–17] Furthermore, animal studies have shown that hyperprolactinemia impairs LH pulse frequency and amplitude, which can, in turn, affect ovulatory function.[5,18] However, the absence of a strong or consistent correlation between prolactin and gonadotropins in our study suggests that these effects may not be reliably captured using single-point hormone measurements in clinical practice.

One of the primary strengths of this study was its large sample size and well-defined patient population, which allowed for robust statistical analysis and subgroup stratification. The inclusion of infertile individuals adds to the clinical depth, as most previous studies did not consider fertility status when evaluating prolactin-related hormonal changes. Furthermore, the strict

Table 1: Descriptive information and hormonal results

	Min–Max	Average±SD
Age	18–46	30.9±6.6
Prolactin	26.13–258.14	43.07±23.25
E_2	5.44–1677	60.48±89.98
P_4	0.01–28	0.68±2.07
TSH	0–40.55	2.29±2.54
LH	0.05–52	5.15±4.15
FSH	0.01–95.49	7.4±7.74
LH/FSH	0.02–25	0.87±1.05
	n	**%**
Diagnosis		
Infertility	638	75.3
Other	209	24.7

Min: Minimum; Max: Maximum; SD; Standard deviation; E_2: Estradiol; P_4: Progesterone; TSH: Thyroid-stimulating hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

Table 2: Correlation between prolactin and other hormones, including LH/FSH levels associated with prolactin concentrations

(n=847)	Prolactin 26–100 mcg/L (n=816)		Prolactin ≥100 mcg/L (n=31)	
	r	p	r	p
E2	-0.084	0.018*	-0.277	0.131
P4	0.074	0.042*	-0.206	0.274
TSH	0.034	0.331	-0.304	0.097
LH	-0.047	0.189	0.105	0.581
FSH	-0.026	0.463	-0.052	0.779
LH/FSH	-0.013	0.713	0.071	0.708

Spearman correlation coefficient *p<0.05. E_2: Estradiol; P_4: Progesterone; TSH: Thyroid-stimulating hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

exclusion of patients with confounding factors such as pregnancy, endometriosis, or incomplete hormonal data increased the internal validity of our results.

However, this study had several limitations. First, its cross-sectional design limits its ability to infer causal relationships or dynamic hormonal interactions. Serum hormone levels were measured at a single time point, which may not accurately reflect the pulsatile nature of GnRH and LH secretion. Second, our study did not include advanced hormonal markers such as kisspeptin or anti-Müllerian hormone (AMH), nor did it evaluate clinical outcomes such as ovulation or pregnancy rates. Finally, etiological subtyping of hyperprolactinemia (e.g., prolactinoma vs. drug-induced vs. idiopathic) was not performed, which may have further clarified hormonal patterns.

Table 3: The correlation between prolactin, other hormones, and LH/FSH levels in relation to infertility

(n=847)	Infertility Prolactin		Other diagnoses Prolactin	
	r	p	r	p
E_2	-0.100	0.012*	-0.166	0.021*
P_4	0.031	0.441	0.077	0.338
TSH	0.066	0.095	0.013	0.854
LH	-0.057	0.150	-0.134	0.066
FSH	0.010	0.806	-0.128	0.071
LH/FSH	-0.064	0.108	-0.029	0.695

Spearman correlation coefficient *p<0.05. E_2: Estradiol; P_4: Progesterone; TSH: Thyroid-stimulating hormone; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone.

CONCLUSION

This study provides valuable insights into the hormonal interplay in hyperprolactinemia by demonstrating that, despite its well-known suppressive effect on the reproductive axis, serum prolactin levels are only weakly correlated with estradiol and not significantly associated with gonadotropin levels in routine clinical settings. These findings suggest that prolactin may impair reproductive function through indirect mechanisms that are not fully captured by static hormone measurements. Future studies should include longitudinal designs, dynamic testing (such as GnRH stimulation or kisspeptin challenge), and clinical outcomes such as ovulation and pregnancy rates to provide a more comprehensive understanding. Stratifying patients according to the etiology of hyperprolactinemia is also critical for identifying subgroup-specific hormonal profiles and guiding individualized therapeutic strategies.

Statement

Ethics Committee Approval: The University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 18.09.2019, number: 86).

Informed Consent: Written informed consent was not required due to the retrospective design and ethics committee regulations.

Conflict of Interest: The authors have no conflict of interest to declare.

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