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ASSOCIATION OF HYPERPROLACTINEMIA IN FEMALES WITH INFERTILITY

Dr Saira Aslam[1], Dr Mona Kanwal Naz[2], Dr Rahat Bibi[3*], Dr Amber Tasnim[4], Dr Sara Umar[5], Dr Surraya Israr[6]

[1]Consultant Gynae & Obs Department, Khalifa Gul Nawaz Teaching Hospital Bannu, Pakistan
[2]Associate Professor of Obstetrics & Gynaecology, Cantt General Hospital Rawalpindi, Pakistan
[3*]Resident Obs & Gynae, Department of Obstetrics & Gynaecolgy, Khyber Teaching Hospital Peshawar, Pakistan
[4]Assistant Professor of Medicine, Abbottabad International Medical College, Pakistan
[5]Specialist Gynea & Obs, Department of Obs & Gynea, Fauji Foundation Hospital (Mailsi), Pakistan
[6]Associate Professor, Department of Obstericts & Gynaecology, GKMC /BKMC Swabi, Pakistan

***Corresponding author:** Dr Rahat Bibi
*Email: Rahatbuner0@gmail.com

Abstract

Introduction: Hyperprolactinemia is an endocrine condition that interferes with ovulation, menstrual periods, and fertility and can affect women. High levels of prolactin inhibit the secretion of gonadotropin and disrupt estrogen levels, which affects the conception rate.

Objectives: The objective of this cross-sectional study is to test the relationship between hyperprolactinemia and infertility in women, report hormonal dysfunctions, and analyze factors affecting BMI and thyroid dysfunction in infertile women.

Materials and Methods: Cross sectional study was carried out at Khalifa Gul Nawaz Teaching Hospital Bannu, Pakistan and Khyber Teaching Hospital Peshawar, Pakistan. Selected subjects were 100 infertile women with hyperprolactinemia and 50 fertile women. It is based on the blood sampling of patients for the assessment of hormonal levels, BMI, thyroid profile, hormonal studied reproductive history etc. To determine the extent to which hyperprolactinemia was related to infertility, statistical tests were conducted.

Results: Infertile women had higher prolactin levels than normal levels ($p < 0.001$), a higher incidence of irregular menses (72%), and an incidence of subclinical hypothyroidism of 40%. TSH and BMI were also found to be higher than normal values of infertility.

Conclusion: Hyperprolactinemia is strongly associated with infertility, based on the disruption of the hormonal balance and metabolic disorders. Prevention, hormone therapy, and changing behavior are crucial to enhance the reproductive success of affected persons.

Keywords: *Hyperprolactinemia, infertility, prolactin, ovulation, thyroid dysfunction, hormonal imbalance, dopamine agonists.*

INTRODUCTION

Elevated blood prolactin concentration, also known as hyperprolactinemia, has, over the years, been established as an important cause of female infertility. Lactogenic hormone, also known as prolactin,

is involved in the process of lactation and other aspects of reproductive systems. Any deviation from this range can lead to menstrual irregularities, anovulation, and, consequently, infertility (1). There has been a lot of concern in the recent past regarding the relationship between hyperprolactinemia and infertility since most women of childbearing age face several reproductive issues. There are many causes of hyperprolactinemia, such as antipsychotic medications, hypothyroidism, pituitary adenomas, and polycystic ovary syndrome (PCOS) (2). Imprecise insights into these relationships are a significant goal in the management of infertility and the preparation of applicable treatment intercessions for women.

The effect of antipsychotic medication on prolactin has been documented since these drugs inhibit dopamine, which is the main inhibitor of prolactin. Long-term low-dose antipsychotic medication use is associated with hyperprolactinemia, menstrual disturbances, and infertility in women (1). Apart from agents that cause drug-induced hyperprolactinemia, other disorders like Sheehan's hypothyroidism are other possibilities. It causes thyrotropin-releasing hormone (TRH) levels to rise, thus releasing prolactin, which interferes with ovulation, hence inadequate fertility (3). Some prior examinations have focused on the relationship between hypothyroidism and hyperprolactinemia in infertile ladies, pointing to the requirement for a complete endocrine examination in such clients (4).

In clinical practice, it has been established that women with hyperprolactinemia are mainly infertile and have not given birth. According to research, women with primary infertility had higher prolactin levels compared to fertile women, indicating that prolactin imbalance could be a leading factor in infertility (5). Moreover, clinical manifestations of hyperprolactinemia among infertile patients include oligomenorrhea, amenorrhea, galactorrhea, and sexual dysfunction (4). As a result of GnRH pulsatility interruption resulting from high levels of prolactin secretion, FSH and LH are not secreted as required to facilitate follicular growth and ovulation (7). This hormonal imbalance typifies the importance of prolactin in the reproductive system and the importance of early diagnosis in infertile women.

In addition to the endocrine aspects, the importance of thyroid function in female fertility has been investigated thoroughly. Hypothyroidism is common in women of childbearing age, and such women experience raised prolactin levels, which poses additional problems regarding their fertility (8). Sex hormones are also involved in the modulation of thyroid hormones, so changes in thyroid hormone levels usually affect the ovarian cycle and fertility. Furthermore, it has been discerned that subclinical hypothyroidism is linked to PCOS and hyperprolactinemia, which point towards inflicting changes in a multiple-factor manner that intensifies the infertility rates in women (9). Therefore, in the diagnosis and treatment of infertility among women, endocrinologists recommend that thyroid profile and prolactin level determinations be carried out to arrive at the right diagnosis.

Regarding hormone variations, fertility, and infertile females have been found to show differences in their levels of prolactin, FSH, LH, estradiol, and TSH (10). The high levels of prolactin in the bloodstream of the infertile female disables normal ovarian function, resulting in anovulation and, consequently, low chances of conception. This paper will also pay some attention to the management of hyperprolactinemia by various caretakers, explicitly focusing on nurses. A clinical trial proved the utility of nursing interventions such as lifestyle changes, medication compliance, and patient counseling in achieving improved fertility in women with hyperprolactinemia (11). These observations underline the need for an interdisciplinary perception and management of hyperprolactinemia associated with infertility.

Some recent research has thus focused on analyzing the influence of prolactin levels on assisted reproductive technologies (ART). According to a study that used a routine cohort review, women with referenced prolactin levels had considerable live birth rates after IVF as compared to those with raised prolactin levels (12). Therefore, it can be concluded that proper regulation of prolactin levels before fertility treatment may lead to high pregnancy outcomes. Further, the correlation between testosterone and prolactin levels has been explored, and it has been established that hormone fluctuations cause infertility among women visiting gynecologists (13). Such studies also imply the significance of the evaluation of hormonal profiles in infertile women. Some of the causal factors to Hyperprolactinemia and infertility have been established in other case-controlled studies, and they include being

overweight or obese, stressful lifestyle, and other medical conditions (14). Hyperprolactinemia has also been reported to be common in subfertile women. A present study has shown that not only subfertile women but also ovulatory women with high plasma prolactin levels have poor fertility treatment outcomes (15). These reports further support the need for early diagnosis and management of Hyperprolactinemia to prevent any further negative impacts on fertility.
Finally, hyperprolactinemia should be considered a serious but frequently disregarded factor in female sterility. This is because of its complexity, which involves the effects of medication, endocrine disorders, and metabolism abnormalities to be diagnosed and treated effectively. Hormonal assessment of such patients and the incorporation of lifestyle changes and specific treatments can go a long way in improving fertility conditions prevalent among women diagnosed with this disease. Therefore, more research studies should be done to discover new therapies and ways of preserving fertility in hyperprolactinemic women wishing to conceive.

Objective: The goal of this study is to examine hyperprolactinemia deficits and determine the correlation of this condition with female infertility, risk factors, hormonal disturbances, and possible therapeutic approaches toward facilitating fertility among affected women.

MATERIALS AND METHODS

Study Design: Cross-sectional study

Study setting: The study was conducted at Khalifa Gul Nawaz Teaching Hospital Bannu, Pakistan and Khyber Teaching Hospital Peshawar, Pakistan

Duration of the study: The study was conducted over six months, from April, 2024 to November, 2024, ensuring adequate time for patient recruitment, data collection, and hormonal assessments.

Inclusion Criteria:

The participants selected in the study were women aged 18 to 40 diagnosed with infertility. Since infertility was the evaluated outcome, the definition used was the failure to conceive for one year with no use of protection. This study only includes patients who were diagnosed with hyperprolactinemia with serum prolactin values above 25 ng/mL. To investigate the role of hyperprolactinemia, patients with regular menstrual cycles, electricity, or idiopathic infertility were enrolled in the study. Such individuals with primary and secondary infertility only were deemed as candidates. Furthermore, the women who agreed to do hormonal profiling such as serum prolactin, thyroid profile, FSH, LH, estradiol, and progesterone.

Exclusion Criteria

The participants of this study included 100 infertile women with hyperprolactinemia and 50 evidently healthy women as a control group from Khalifa Gul Nawaz Teaching Hospital Bannu, Pakistan and Cantt General Hospital Rawalpindi, Pakistan. The patient questionnaire included the traditionally defined AI components of menstrual cycles, galactorrhea, thyroid dysfunctions, and medication history. Measurement tools were also obtained, including body weight, height, and body mass inlined. Venous blood was collected on days 2–5 of the menstrual cycle to estimate serum prolactin, FSH, LH, TSH, free thyroxin, estradiol, and progesterone determined by CLIA. The use of MRI or CT scans was advised for presumed pituitary disease. Descriptive statistics were performed in SPSS version 25 to analyze the correlation between hyperprolactinemia and infertility using the Chi-square test and Pearson correlation coefficient. The results were considered statistically significant at $p< 0.05$. The study was approved by the Human Research Ethics Committee of the Hospital's IRB.

Methods

Patients presenting with EP features to the outpatient department are included after completing written consent. TVS and TAUS were performed by one experienced radiologist with > 5 years of experience

on every patient. Findings following both modalities were noted, including an adnexal mass, fetal cardiac activity, free fluid in the pouch of Douglas, or a tubal ring. All patients were subjected to an ultrasound test, and then a laparotomy was performed by a qualified obstetrician to confirm the diagnosis of EP. The laparotomy findings were used as a reference to compare the findings made through laparotomy. Storage of patient findings, ultrasound reports, and laparotomy reports was structured proforma based on the previous design. The systematic data collection procedure was done to minimize inter-observer variability. Statistical Package for Social Sciences (SPSS) version 20 was used to analyze data.

RESULTS

A total of 100 infertile women with hyperprolactinemia were studied as a group, along with 50 fertile women as controls. The control group had a mean age of 28.7 ± 5.1 years, and the mean age of infertile women was 29.4 ± 4.8 years. The two groups were not statistically significantly different in age (p = 0.42). Despite this, it was found that the infertile women (BMI 27.8 ± 3.5 kg m2) had a significantly higher mean BMI (p < 0.001) than the control group (BMI 24.5 ± 2.8 kg m2).

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Infertile Women (n=100)	Fertile Women (n=50)	p-value
Age (years)	29.4 ± 4.8	28.7 ± 5.1	0.42
BMI (kg/m²)	27.8 ± 3.5	24.5 ± 2.8	<0.001
Duration of Infertility (years)	3.6 ± 1.4	—	—
Presence of Galactorrhea (%)	38 (38%)	4 (8%)	<0.001
Menstrual Irregularities (%)	72 (72%)	10 (20%)	<0.001

The control group contained only 20% who had menstrual irregularities, while 72% of infertile women had menstrual irregularities (p < 0.001). Of infertile women, 38% reported galactorrhea and only 8% of fertile women reported galactorrhea (p < 0.001).

Serum prolactin analysis revealed significantly higher values of serum prolactin in the infertile group (45.2 ± 8.6 ng/mL) vs. the fertile women (15.8 ± 3.9 ng/mL, p < 0.001). Furthermore, the FSH, LH, and estradiol levels in infertile women were also significantly abnormal, demonstrating ovarian dysfunction.

Table 2: Hormonal Profile of Study Participants

Hormone	Infertile Women (n=100)	Fertile Women (n=50)	p-value
Prolactin (ng/mL)	45.2 ± 8.6	15.8 ± 3.9	<0.001
FSH (mIU/mL)	6.1 ± 1.5	7.2 ± 1.2	0.002
LH (mIU/mL)	4.8 ± 1.1	6.3 ± 1.4	<0.001
Estradiol (pg/mL)	28.5 ± 6.9	38.7 ± 5.3	<0.001

The vast majority of infertile women with subclinical hypothyroidism had subclinical hypothyroidism (40%) and had higher prolactin levels. The results revealed significantly higher TSH levels in the infertile group as compared to fertile women (p = 0.004).

Table 3: Thyroid Function in Infertile and Fertile Women

Thyroid Parameter	Infertile Women (n=100)	Fertile Women (n=50)	p-value
TSH (mIU/L)	4.9 ± 1.7	2.3 ± 0.8	0.004
FT4 (ng/dL)	0.88 ± 0.15	1.2 ± 0.11	<0.001
Subclinical Hypothyroidism (%)	40 (40%)	8 (16%)	<0.001

Lastly, hyperprolactinemia was reported to have a significant correlation with irregular menstruation, ovulation abnormalities, and thyroid disorders among infertile women. This study has pointed to the fact that hormonal imbalances, especially of prolactin-stimulating hormone and abnormal thyroid function, are likely to be associated with infertility. These findings suggest the importance of calling for screening and timely management in women with reproductive issues.

DISCUSSION

Hyperprolactinemia is known to have detrimental effects on female fertility with regard to ovulation, menstrual cycles, and fertility in general. The results of the present research again confirm the strong link between hyperprolactinemia and female infertility because many of the participants exhibit menstrual abnormalities, ovulatory disorders, and galactorrhoea. The results also show the association between hyperprolactinemia and thyroid dysfunction, including subclinical hypothyroidism, to suggest an interconnection of the hormonal pathways in the reproductive system. The hormonal changes were proven to show that infertile women had significantly higher levels of serum prolactin when compared to the fertility group. This concurs with the past studies done that have shown a direct inhibitory effect of hyperprolactinemia on the hypothalamic-pituitary-ovarian (HPO) axis, which results in disturbed gonadotropin release, anovulation, and luteal phase disruption (1). It inhibits the pulsative secretion of GnRH, which inhibits FSH and LH secretion, and this may lead to the impairment of follicular development and ovulation (2). This mechanism illuminates why the intensity of LH and FSH in hyperprolactinemic infertile women was considerably lower in the present investigation.

Another observation of the study was that 72 % of the infertile women with hyperprolactinemia had irregular menstruation compared to 20% of the normal group women. Previous research has clearly shown that hyperprolactinemia delays the follicular phase, and the ovary does not undergo a luteal phase transformation during menstrual cycle 3. In some circumstances, it may result in an absence of menstruation, below referred to as anovulation, which affects conception (4). This provokes the need to perform a prolactin level check on any woman presenting with menstrual irregularities because the two are correlated. Furthermore, they also analyzed galactorrhea, which was found to be present in 38% of infertile women, while it was present in only 8% of the control group. Regarding this finding, other studies also point to the effect of chronic hyperprolactinemia, which results in the overproduction of breast milk in non-lactating females (5). It is also important to realize that not all women with hyperprolactinemia display galactorrhea to warrant the measurement of serum prolactin in diagnosing this condition. However, hyperprolactinemia, in this case, needs to be further investigated for pituitary tumors since prolactinoma is the most frequent cause of galactorrhea.

The present study showed that thyroid dysfunction, including subclinical hypothyroidism, is positively related to hyperprolactinemia. Infertility women had subclinical hypothyroidism in the 40% level, which is higher than that found among the fertile women at 16%. This will support the proposition that thyroid dysfunction leads to reproductive disorders due to the modulation of prolactin secretion (7). Thyroid deficiency results in increased secretion of thyrotropin-releasing hormone (TRH) and consequent hyperprolactinemia of secondary origin (8). Therefore, thyroid screening has to be one of the tests included in the differential diagnosis of women with infertility coupled with hyperprolactinemia. It was observed that BMI was higher in cases of hyperprolactinemic infertile women than those in the control group. This is important since obesity is particularly known to disrupt the hormonal equilibrium in the body, one of them being insulin resistance, which could worsen hyperprolactinemia in the body (9). In addition, one finds that obesity causes polycystic ovary syndrome (PCOS), which, like Endometriosis, is another endocrine disorder that is related to infertility in women (10). Another work reported that hyperprolactinemia and PCOS are both linked to similar metabolic dysfunctions, which make the latter worse (11).

The role of hyperprolactinemia on assisted reproductive technologies (ART), including in vitro fertilization (IVF), has also been considered beyond natural conception. Recent studies have shown that women with well-controlled prolactin levels have significantly improved live birth rates

following IVF compared to women with persistently elevated prolactin levels (12). The implication is that ART would be more successful if hyperprolactinemia is controlled first. Clinical experience with dopamine agonists like bromocriptine and cabergoline has demonstrated their ability to restore ovulatory function and improve pregnancy rates (13). However, a noninvasive and effective treatment strategy for hyperprolactinemia-induced infertility has been introduced, and dopamine agonists have been used as first-line therapy in these patients.

Hyperprolactinemia is well known to be associated with infertility, but many cases are idiopathic, meaning that prolactin levels are elevated with no known cause. The clinical management of these cases is complicated because underlying conditions such as pituitary tumors, hypothyroidism, or drug-induced hyperprolactinemia cannot be treated. Studies of genetic and environmental factors may be needed to explore whether hyperprolactinemia is an idiopathic disorder (14). However, certain limitations should be acknowledged while this study shows important associations. The cross-sectional design also does not establish a causal relationship between hyperprolactinemia and infertility. Second, although the sample size was sufficient to detect statistical differences, a more extensive multicenter study would give stronger conclusions. Further, follow-up on the effects of prolactin-lowering treatments on fertility outcomes in the long term is also needed.

Finally, this study confirms the strong association between hyperprolactinemia and infertility in women by identifying significant hormonal imbalance, menstrual irregularities, and thyroid dysfunction. The findings stress the importance of early screening, modifications in lifestyle, and conservative medical treatment to improve reproductive outcomes in hyperprolactinemic women. Healthcare providers can improve women's fertility potential by combining dopamine agonist therapy, thyroid management, and weight control strategies. Future research should focus on the long-term fertility consequences of hyperprolactinemia treatment and its effect on pregnancy rates in assisted reproductive technologies.

CONCLUSION

The results of this study point out the strong correlation between hyperprolactinemia and female infertility and the consequences of hypoestrogenism and hypothyroidism for disturbances in menstruation and ovulatory function. High prolactin levels in serum interfere with the function of the hypothalamic-pituitary-ovarian axis and cause irregularity in the development of follicles and anovulatory cycles. Subclinical hypothyroidism was present in a substantial proportion of infertile women, further supporting the need for estimation of thyroid function in hyperprolactinemic patients. Higher BMI is also seen in infertile women and may represent a metabolic link between obesity, metabolic imbalance, and reproductive failure. The current study highlights the need for early diagnostic and preventive measures, hormonal control, as well as lifestyle measures to enhance the fertility rate in women with hyperprolactinemia. Therapeutic strategies for the restoration of reproductive function include dopamine agonists, weight management, and thyroid treatments. Future research should evaluate the long-term fertility outcome following prolactin-lowering therapy and the role of prolactin in amplifying the pregnancy success rates in natural and assisted reproductive technologies. Hyperprolactinemia management in clinical practice can rescue reproductive health and infertility management.

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