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Association of Hyperprolactinemia in Females with Infertility

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ABSTRACT

Introduction: Hyperprolactinemia is one of the most frequent endocrinological disorders in women that affects the hypothalamic-pituitary gonadal axis, resulting in infertility. It plays a crucial role in reproductive disorder outcomes aligned with hormonal irregularity, PCOS, and thyroid disorders. **Objectives:** Consequently, to explore the correlation between hyperprolactinemia and female infertility with a focus on hormonal and metabolic changes, as well as on comorbidities like PCOS and hypothyroidism. **Materials and Methods:** The present study was a cross-sectional study carried out Department of Gynaecology and Obstetrics, District Headquarter Teaching Hospital/ Gomal Medical College, Dera Ismail Khan, Pakistan in the duration from January, 2024 to June, 2024. One hundred fifty infertile women aged 18–40 across the general outpatient clinic were recruited, and 78 had hyperprolactinemia. Clinical and hormonal data samples were taken and processed using the Statistical Package for Social Sciences (SPSS). **Results:** Hyperprolactinemia was meaningfully correlated with menstrual abnormalities, PCOS, and hypothyroid problems. Infertile women in their study had significantly increased prolactin levels, which resulted in lower levels of LH, FSH, and estradiol and higher levels of BMI, as well as insulin resistance. **Conclusion:** Hyperprolactinemia causes hormonal and metabolic alteration and affects female fertility. Hearing and treatment at an early stage of fertility problems and comprehensive therapeutic intervention may enhance fertility.

INTRODUCTION

Hyperprolactinemia is an endocrine disorder that refers to excessive levels of prolactin in the body. It is a hormone secreted by the anterior pituitary gland and is essential in female fertility and breastfeeding. High prolactin may interfere with the regulation of the hypothalamic-pituitary-gonal act, which is a significant cause of infertility in women. The etiology of this condition may be physiological, pathological, or pharmacologically induced, and it is involved in several reproductive disorders, such as amenorrhea, anovulation, and galactorrhea (1). The link between hyperprolactinemia and infertility is complex because, in addition to hormonal disturbances, there are predictive factors like PCOS and thyroid disorders, which should be discussed in detail to enhance the diagnostic and therapeutic management of women with this condition. A study has also indicated that hyperprolactinemia leads to infertility, and worse affected parties are women who use antipsychotic products. Some drugs make dopamine not inhibit prolactin secretion, leading to high prolactin in the body and influencing the ovaries and fertility (1). Moreover, infertile women also suffer from PCOS, in which hyperprolactinemia is an associated phenomenon with insulin resistance and impaired beta-cell function. These metabolic disturbances affect ovulatory cycles and as reproductive issues' worsen. These interactions confirm the fact that treatment of hyperprolactinemia entails several hormonal problems in women with PCOS, PRL, and insulin resistance.

Hypothyroidism is the other significant cause linked with the prolactin level increase and infertility. Primary hypothyroidism, which indicates a deficiency of thyroid hormones, is found in women with primary and secondary infertility. It could raise thyrotropin-releasing hormone (TRH) levels through the hypothalamus and lead to a condition known as hyperprolactinemia (3). The hormones described above underscore the need to assess thyroid function in women with infertility since treatment of thyroid dysfunction can enhance fertility. Furthermore, the complexity of the prolactin–thyroid

hormones interaction and its effect on fertility has been described thoroughly, with a focus on which an interdisciplinary approach to the management of infertility in women with hyperprolactinemia is warranted (4). Protein studies revealed alterations in the hormonal environment of infertile women, including prolactin, thyroid hormones, LHF, FSH, estradiol, and progesterone, whose disturbed balance also contributes to the problem of infertility (5). Various scientific researches have indicated a strong relationship between these hormones. Therefore, it can be seen that hyperprolactinemia influences the reproductive hormones in a roundabout way (5). For example, hyperprolactinemia may reduce gonadotropin-releasing hormone GnRH pulse frequency with a subsequent decrease in LH and FSH release necessary for follicular growth and ovulation (6).

They found a high frequency of hyperprolactinemia in infertile women and an increased prevalence of this condition in euthyroid women. This fact implies that an increased secretion of prolactin may cause infertility even if no thyroid disease is observed (7). Additionally, data from institutions have shown a strong correlation between prolactin levels and female infertility and the need to have prolactin estimation in every fertility evaluation (8). Hyperprolactinemia, together with subclinical hypothyroidism and PCOS, proves the close interconnections of hormonal signaling, which have to be targeted to improve female fertility (9). Subsequent clinical studies have also extended the observations about hypothyroidism, hyperprolactinemia, and female fertility with greater detail on the pathophysiology of these disorders as well (10). Even when hyperprolactinemia is mild and seen in the context of a couple's infertility or subfertility, some data suggest it influences fertility (11). Researchers have reported variations in prolactin, FSH, LH, estradiol, and TSH between infertile and fertile women, aspects that support the usefulness of hormonal biomarkers to diagnose factors leading to infertility (12).

Furthermore, previous studies have found that the prolactin level in the bloodstream of infertile women is related to thyroid hormone levels, and it can be assumed that these two endocrine systems are interactive (13). Several more case-control studies have pointed to various risk factors for infertility in women, such as hyperprolactinemia, and the need for critical evaluation of multiple factors causing infertility (14). Prolactin also affects fertility; from a study done evaluating total testosterone and free testosterone in infertile females, elevated prolactin level was a known cause of infertility (15). The complex interaction between hyperprolactinemia and the problem of infertility requires further investigation and clarification of the diagnostic and treatment approaches. Some hormonal dysfunctions, such as hyperprolactinemia, can be detected by hormonal testing, and prolactin levels and thyroid function tests should be included in infertility evaluation. This paper has discussed the prevalence and effects of hyperprolactinemia as well as other conditions that affect fertility and recommended ways through which clinicians can better fertility results and the lives of affected women.

OBJECTIVE

To explore the relationship between hyperprolactinemia and infertility in females with particular emphasis on hormonal alterations, associated diseases including PCOS and thyroid disorders, as well as the reproductive performance of women with hyperprolactinemia

MATERIALS AND METHODS

Study Design: This paper used a cross-sectional approach to establish the relationship between elevated prolactin levels and infertility among females.

Study setting: This research was conducted at the Department of Gynaecology and Obstetrics, District Headquarter Teaching Hospital/ Gomal Medical College, Dera Ismail Khan, Pakistan in the duration from January, 2024 to June, 2024

Duration of the study: Duration from January, 2024 to June, 2024.

Inclusion Criteria

The participatory criteria for this study included all patients between the ages of 18 and 40 who presented with primary infertility. Study subjects had to be suffering from hyperprolactinemia, as verified by laboratory values of prolactin greater than 25ng/mL. Further, only respondents who provided informed consent and agreed to participate in the study were enrolled.

Exclusion Criteria

Preliminary incorporation criteria were created, and exclusion criteria were set strictly to control the noise. Pituitary tumor patients with known aetiologies of hyperprolactinemia were excluded, as were women using an anti-psychotic medication, which can increase prolactin levels. Postmenopausal women were excluded because hormonal fluctuations during pregnancy and lactation affect mineral bone density. Additionally, those with undiagnosed hypothyroidism or other endocrine disorders or with other systemic diseases were not included in the study, isolating the effects of hyperprolactinemia on infertility.

METHODS

In this study, an attempt was made to determine the correlation between hyperprolactinemia and female infertility by collecting clinical data and conducting laboratory tests. Only patients who fulfilled the inclusion criteria were selected in this case through convenience

sampling, and these included mainly female patients from attending gynecology and endocrinology OPD at Department of Gynaecology and Obstetrics, District Headquarter Teaching Hospital/ Gomal Medical College, Dera Ismail Khan, Pakistan in the duration from January, 2024 to June, 2024. Informed also consent, questions regarding reproductive history, irregularities of menstrual cycles, and earlier treatments of infertility were documented. Blood was collected also in vane for serological prolactin determinations and to assess other hormonal variables like TSH, LH, FSH, and estradiol. Serological hormonal measurements were performed using chemiluminescent immunoassay methods in laboratory tests. Statistical analysis was conducted with SPSS Statistics. Mean, median, mode, range, standard deviation, and percentage were used to present demographic and clinical data. Statistical comparisons were conducted to examine the relationship between hyperprolactinemia and infertility with a chi-squared test and logistic regression analyses with $p < 0.05$.

RESULTS

One hundred and fifty infertile women aged 30 – 45 years were involved in the study, with a mean age of 29.5 ± 5.8 years. Among these, 78, forty-two, and 30 were diagnosed to have hyperprolactinemia with serum PRL greater than 25 ng/mL. The rest 72 (48%) had normal prolactin levels in their blood samples. Data regarding the demographic and clinical profiles of the participants are described in Table 1.

Table 1

Demographic and Clinical Characteristics of Participants

Variable	Hyperprolactinemia (n = 78)	Normal Prolactin (n = 72)	p-value
Age (years)	30.2 ± 5.6	28.8 ± 6.0	0.15
BMI (kg/m²)	27.5 ± 4.2	24.8 ± 3.9	<0.01
Duration of infertility (years)	4.1 ± 1.7	3.5 ± 1.5	0.02

Hyperprolactinemia was identified to be strongly related to menstrual abnormalities; 65 of the 78 women with raised prolactin had oligomenorrhea or amenorrhea compared to 28 of 71 control women ($p < 0.01$). Hormonal profiles indicated that the women with hyperprolactinemia had significantly lower LH and FSH levels and substantially lower estradiol levels than the controls Table 2.

Table 2

Hormonal Profiles of Participants

Hormone	Hyperprolactinemia (n = 78)	Normal Prolactin (n = 72)	p-value
Prolactin (ng/mL)	36.8 ± 10.5	15.4 ± 3.2	<0.01
LH (mIU/mL)	4.5 ± 1.8	6.2 ± 2.1	<0.01
FSH (mIU/mL)	5.1 ± 1.7	7.0 ± 2.3	<0.01
Estradiol (pg/mL)	40.5 ± 12.6	55.8 ± 15.3	<0.01

Concurrent diseases, including PCOS and hypothyroidism, were also reported in women with hyperprolactinemia compared to normal controls. PCOS was detected in 42.3% of cases with hyperprolactinemia and 15.3% of women in the group with normal prolactin levels ($U = 32$, $p < 0.01$). In hyperprolactinemic women, subclinical hypothyroidism was detected in 35.9% of women compared with 12.5% of women in the regular prolactin group ($p < 0.01$). These associations are summarized in Table 3.

Table 3

Associated Conditions in Study Participants

Condition	Hyperprolactinemia (n = 78)	Normal Prolactin (n = 72)	p-value
PCOS (%)	42.3	15.3	<0.01
Subclinical Hypothyroidism (%)	35.9	12.5	<0.01

The findings manifest the close link between hyperprolactinemia and infertility caused by hormonal disorders and related diseases, such as PCOS and hypothyroidism. These results point to a need for better diagnostic and treatment emphasis on individual sub-fertile women for enhanced chances of conception.

DISCUSSION

High prolactin level is a significant endocrine imbalance that affects the female reproductive cycle and fertility through several pathways. The purpose of this paper was to review studies regarding hyperprolactinemia and infertility, especially concerning hormones, metabolism, PCOS, and hypothyroidism. Therefore, supporting the proposed hypothesis, the findings contribute fresh knowledge to the associations between hyperprolactinemia and reproductive disorders. Hyperprolactinemia was found to be rather frequent in infertile women, and the same is in line with the literature, which confirms that it serves as an important causative factor for infertility (1). High prolactin concentration directly affects the hypothalamic-pituitary gonadal axis by suppressing gonadotropin-releasing hormone GnRH pulse generation, resulting in a low secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This hormonal disruption leads to anovulation and is one of the most common causes of infertility in women with hyperprolactinemia (5). Additionally, women with hyperprolactinemia had significantly reduced estradiol levels, supporting previous research that estrogen synthesis is negatively influenced by high prolactin (4).

Another important finding that can be mentioned is hyperprolactinemia and the irregularity in the menstrual cycle. The majority of the hyperprolactinemic women in this study suffered from oligomenorrhea or amenorrhea. This result is consistent with a previous study that states

that menstrual dysfunction is a characteristic feature of hyperprolactinemia-associated infertility (7). These irregularities are due to prolactin's action on the ovaries, suppressing normal follicular growth and ovulation. Moreover, it was identified hyperprolactinemia has a complex relationship with PCOS, another endocrine abnormality that can lead to infertility. The rate of PCOS was considerably higher in hyperprolactinemia than in normal prolactin women, which underlined the reciprocal association between these conditions (6). Raised prolactin can even worsen other hormonal dysfunctions typical for PCOS, like hyperandrogenism and increased insulin resistance, which would all but exacerbate the chances of conception (9). Low-grade inflammation that characterizes PCOS could be promoting prolactin secretion, leading to a vicious cycle of reproductive disorder (2).

Another coexisting medical condition found in hyperprolactinemic women was thyroid dysfunction, which was a common type of subclinical hypothyroidism. The higher rate of hypothyroidism in this group is consistent with previous works reporting that thyroid dysfunction is associated with hyperprolactinemia (3). Hyperthyroidism results in decreased TRH plasma levels, and there is evidence pointing to thyroid dysfunction as involved in the pathogenesis of hyperprolactinemia (8). It is essential to manage thyroid dysfunction as it can be a contributing factor to poor fertility since correcting thyroid disorders can help decrease prolactin secretion and help regain regular cycles. Another aspect of hyperprolactinemia intervention on fertility was revealed to be metabolic disorders in patients. Prior studies have also shown that women with a high level of prolactin had higher BMI and insulin resistance that contributes to infertility (12). This effect of hyperprolactinemia on the metabolic parameters might be attributed to its impact on the insulin signaling pathways since other studies have reported a relationship between prolactin and insulin resistance in PCOS patients (2, 6). Such results emphasize the need to focus on multiple aspects of infertility treatment associated with hyperprolactinemia, including both hormonal and metabolic factors.

Hyperprolactinemia accompanied by hypothalamic-pituitary axis dysfunction is also an important topic. Hyperprolactinemic states are often due to benign pituitary adenomas, referred to as prolactinomas, which, if untreated, can result in significant reproductive and metabolic morbidity (1, 11). Even though prolactinomas per se were not considered in this investigation, their relation to hyperprolactinemia as a cause of infertility necessitates imaging studies in cases of sustained hyperprolactinemia. If diagnosed at an early stage, the effects of prolactinomas on fertility and general well-being can be lessened when treatment is administered immediately. Pharmacological treatment of hyperprolactinemia has been rising in the last decade, and it has been widely effective in enhancing fertility rates. The first-line medications for hyperprolactinemia are dopamine agonists, including bromocriptine and cabergoline, that significantly decrease prolactin levels and reintroduce ovulation in the vast majority of patients (1, 11). These medications act by blocking dopamine's inhibitory effect on prolactin release and correcting the root of the problem. However, their use needs close monitoring for side effects profile and contraindication, mainly when used in women with PCOS and hypothyroidism.

Other relevant strategies for hyperprolactinemia patients are weight loss and dietary changes. Obesity aggravates hormonal and metabolic derangements, which in turn leads to the development of a cycle of infertility (12). Dietary and exercise interventions have improved insulin sensitivity, decreased prolactin concentrations, and better ovulatory activity in hyperprolactinemic-affected women. Therefore, Lifestyle changes are recommended to complement the medical management of infertility in this population. The results of the present research support and expand the current concept of hyperprolactinemia and recurrent miscarriage, referring to complex diagnostic and therapeutic approaches. Protein yields should be performed periodically as part of infertility testing in women with irregular menstruation, PCOS, or thyroid disease. To reduce the effect on fertility, early diagnosis or any intervention then can help in handling hyperprolactinemia.

This study has brought out some valuable results. However, there are certain limitations to this study. Limitations include the lack of ability to make causal inferences due to the cross-sectional design of the studies and the exclusion of potential patients with conditions like prolactinomas, which deprives the analysis of actual external validity. Further studies of the topic should employ longitudinal research and encompass a larger group of hyperprolactinemic individuals so that the effects of this disorder on fertility can be better comprehended. Lastly, hyperprolactinemia is a complex neuroendocrine disease with a significant impact on women's reproductive function. Issues with hormonal and metabolic disorders, together with the existence of other disorders such as polycystic ovary syndrome and hypothyroidism, present infertility in this group as a challenge to manage. Medical management, together with lifestyle changes and selective therapy, will increase the success in fertility and overall well-being of women with PCOS.

CONCLUSION

The present work addresses the possible connection of hyperprolactinemia as a factor affecting fertility in women and its impact on the hypothalamic-pituitary-

gonadal axis and hormonal and metabolic disorders. High prolactin levels interfere with ovulation, worsening conditions like PCOS and hypothyroidism, disrupting the menstrual cycle, and metabolic disorders, all of which are antifertility. In the topic of hyperprolactinemia, treatment approaches entail prolactin level monitoring, dopamine agonists in particular, alongside treatment of other related disorders such as hypothyroidism and PCOS. Different aspects of lifestyle, such as dietary habits, also improve fertility outcomes when combined with weight change since metabolic risk factors contribute to subfertility. Although these data help suggest how hyperprolactinemia influences infertility, more longitudinal work must be done to determine cause and effect and specific management protocols. However, Timely diagnoses and several ways of treatment allowing to return reproductive function and enhance the quality of life in women are crucial.

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