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STATUS OF THYROID AND PROLACTIN HORMONE LEVELS AMONG PRIMARY INFERTILITY PATIENTS

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Abstract:

Objective: *Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Hyperprolactinemia and thyroid dysfunction are associated with reproductive dysfunction and infertility. Hypothyroidism and hyperprolactinemia are found to be closely interrelated. This study aimed to observe the level of serum prolactin, free Tri-iodothyronine (fT3), free Thyroxine (fT4) and Thyroid stimulating hormone (TSH) in women with primary infertility and to correlate the level of serum prolactin with TSH.* ***Methods:*** *The study was conducted on patients visiting OPD because of infertility at the Medicine and Gynecology and Obstetrics department of Services Hospital Lahore for one year duration from May 2019 to May 2020. The study included 50 women with primary infertility and 50 healthy controls of same age. Serum prolactin, fT3, fT4 and TSH levels were measured in all subjects.*

Results: *The mean age of participants was 26.8 years. The median serum prolactin (21.8) and TSH levels (4.5) were found to be significantly high in the case group ($p<0.001$). Out of the total subjects with hyperprolactinemia, 51.1% were found to have hypothyroidism. There was a moderately strong, positive and significant correlation between serum prolactin and TSH levels ($r=0.62$, $p<0.05$). ROC curve analysis showed that at a cutoff value of 22.5 ng/ mL for serum prolactin, a sensitivity of 86% and specificity of 82% could be achieved for detecting hypothyroidism.*

Conclusion: *The high incidence of hyperprolactinemia and thyroid disorders in primary infertility underlines the fact that all women coming to consult for infertility should be advised to undergo thyroid function tests and assess prolactin in the early stages of infertility control.*

Key words: *infertility, hyperprolactinemia, hypothyroidism*

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INTRODUCTION:

According to the International Monitoring Committee for Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility is a disease of the reproductive system that is defined by the inability to perform a clinical pregnancy after 12 months or more. Primary infertility is used to refer to a couple who have never been pregnant, despite intercourse and regular sexual intercourse, and secondary infertility is used for couples who have had at least one pregnancy, even if they ended in abortion. Around 8-12% of couples worldwide experience some form of infertility throughout their reproductive lives. This led to the acceptance of infertility as a public health problem. The cause of infertility cannot be explained in 45% of female couples, 30% of male infertility and the remaining 25%. Hyperprolactinemia, the presence of abnormally high levels of prolactin in the blood, is the most common endocrine disorder of the hypothalamic-pituitary axis, and its occurrence ranges from 0.4% to 9-17% in the normal normal adult population. Excessive prolactin secretion in women with reproductive disorders reduces the pulsatile release of gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH), causing reproductive dysfunction and infertility. Other disorders such as amenorrhea and galactorrhoea. Thyroid dysfunction reduces the risk of pregnancy, and also negatively affects the course of pregnancy.

Hypothyroidism is associated with a wide range of reproductive disorders, from abnormal sexual development to menstrual disorders and infertility. Hypothyroidism and hyperprolactinemia are closely related. Because the hypothalamus thyrotropin releasing hormone (TRH) increases the secretion of TSH and prolactin, serum prolactin levels may increase in cases of hypothyroidism. This study evaluated prolactin and thyroid hormone levels in patients with primary infertility.

PATIENTS AND METHODS:

It was a cross-sectional study held in the Medicine and Gynecology and Obstetrics department of Services Hospital Lahore for one year duration from May 2019 to May 2020. The study involved 50 women with primary infertility between 20 and 35 years old, and 50 healthy women of proven fertility at the same age were included as controls. Exclusion criteria adopted during the selection of the case were male infertility, anatomical abnormalities that interfered with fertilization and implantation of the genitourinary system and treatment of thyroid disorders and hyperprolactinemia. This work was approved by the Institutional Review Board. Informed consent was obtained from all participants and the relevant history recorded. Serum prolactin, fT3, fT4, and TSH were estimated using the fully automated Enhanced Chemiluminiscent Immunoanalyzer (ECi). Laboratory standard operating procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot, for the validation of the results. The data was analyzed in the social science statistics package (SPSS Inc, Chicago, Illinois, USA, version 20). An independent T-test and Mann-Whitney U test were used to compare the mean and median between the 95% confidence interval (CI) between the case and control group. It was significant at $p < 0.05$.

RESULTS:

Of the 100 selected patients, 50 were 27.2 ± 3.89 years old and 50 were control age 26.56 ± 2.75 years ($p > 0.05$). Maximum percentage of items; 50% in this case and 54% in the control group were found at the age of 26-30 years. Most of the subjects in both groups were euthyroid (54% in cases and 88% in the control group). Subclinical hypothyroidism was found in 36% of cases and 12% in the control group. Only 2% had hyperthyroidism in the case group. Among the cases, 68% and among the control group 22% of women had elevated prolactin levels (Tables 1 and 2).

Table 1 Thyroid hormone status among the case and control group

Parameters	Case (n=50)	Control (n=50)	Total (n=100)
Euthyroid	27 (54%)	44 (88%)	71
Subclinical hypothyroid	18 (36%)	6 (12%)	24
Hypothyroid	4 (8%)	0 (0%)	4
Hyperthyroid	1 (2%)	0 (0%)	1
Total	50 (100%)	50 (100%)	100

Table 2 Distribution of prolactin in case and control group

Prolactin	Case (n=50)	Control (n=50)	Total (n=100)
Normal	16 (32%)	39 (78%)	55
High	34 (68%)	11 (22%)	45
Total	50 (100%)	50 (100%)	100

The mean serum fT4 value was lower in the cases compared to the controls (13.94 ± 4.95 in the cases and 16.09 ± 3.22 in the controls, p <0.05). However, mean fT3 values did not differ significantly between cases and controls (p = 0.16). The difference between mean TSH (4.5 in cases compared to 2.4 in the control group) and prolactin (21.8 in cases compared to 11.2 in the control group) was statistically significant (p <0.05, Manna -Whitney) (Table 3).

Table 3 Comparison of serum TSH and prolactin among case and control group

Hormone	Case		Control		p-value
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
TSH (0.46-4.68 µIU/mL)	8.31 ± 17.84	4.5 (0.02-100)	2.67 ± 1.28	2.4 (1.2-5.9)	<0.001
Prolactin (3-18.6 ng/mL)	25.09 ± 14.86	21.8 (5.8-92.1)	13.09 ± 5.43	11.2 (5.9-23.9)	<0.001

45 out of 100 participants had hyperprolactinemia, 23 of them increased TSH levels, indicating that the incidence of hypothyroidism was 51.1% in women with hyperprolactinemia (Table 2). Spearman's correlation showed a moderately strong, positive and significant correlation between serum prolactin levels and TSH levels between cases (r = 0.62, p <0.05). Analysis of the ROC curve showed that at a cut-off value of 22.5 ng / ml for serum prolactin, 86% sensitivity and 82% specificity could be obtained to detect hypothyroidism (AUC = 0.856, upper limit lower limit CI 0.74 , 0.96) (Fig. 1).

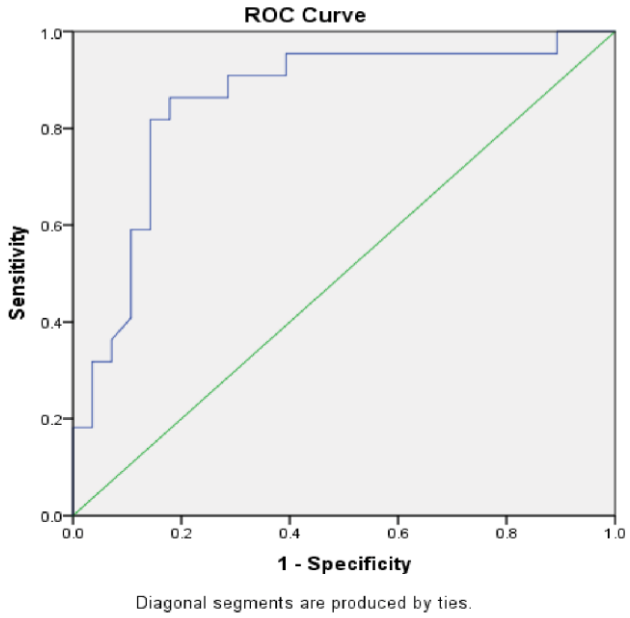

Figure 1 ROC curve for cases

DISCUSSION:

This study was conducted to measure thyroid hormone and prolactin levels in patients with primary infertility and to compare results from people with confirmed fertility. Infertility is a serious life crisis for a large number of people, touching them as individuals, marriage partners, and family members and society. Hyperprolactinemia is a common symptom of reproductive disorders and is an important reason for ovulation and infertility in women. Because it is understood that excessive prolactin secretion not only causes abnormalities such as galactorrhoea and amenorrhea, but also leads to infertility, prolactin prognosis is made for patients who come to the clinic because of difficulties in conceiving. Thyroid hormone levels also affect fertility levels. It is known that thyroid dysfunction causes many different reproductive disorders in which patients with infertility must assess thyroid hormones. In this study, serum prolactin levels increased in 68% of infertility cases; this is Prathibha et al. (41%), Hymavathi et al. (37%), Emokpae et al. (33.7%) and Olooto et al. (28%). The incidence of hyperprolactinemia in women with infertility was slightly lower in Verma et al. (18.27%) and Agrawal et al. (11.5%). Stress is partly a contributing factor to hyperprolactinemia, which can be attributed to one of the factors determining the variable frequency of patients with hyperprolactinemia in various studies.

People in the control group had prolactin levels in the range of 5.9 ng / ml to 23.9 ng / ml, 22% had hyperprolactinemia. Stress during puncture may lead to a transient increase in prolactin levels, which may be a factor contributing to the hyperprolactinemia observed in the control group. Microadenoma occurs in less than 10% of patients with idiopathic hyperprolactinemia. In this study, none of the hyperprolactinemia cases were higher

than 100 ng / ml. Pituitary adenoma usually occurs as a cause of hyperprolactinemia in patients with serum prolactin values above 100 ng / ml. In this study, the presence of adenoma is less likely in people with hyperprolactinemia, because the level of prolactin is less than 100 ng / ml. Thyroid dysfunction disturbs female reproductive physiology because it can cause infertility. The ovaries respond to thyroid hormones due to the presence of thyroid hormone receptors in human oocytes. Thyroid hormones are also synergized with human chorionic gonadotropin (hCG) receptor mediated by FSH to exert a direct stimulatory effect on granular cell function (progesterone production) and in vitro studies have been shown. Impact on trophoblast differentiation. Another way of hypothyroidism on fertility is by changing peripheral estrogen metabolism and reducing the production of sex hormone binding globulin (SHBG). Most thyroid dysfunction in the study population is subclinical hypothyroidism (24%). The incidence of subclinical hypothyroidism in women with infertility ranges from 0.7% (Shalev et al.) To 43% (Gerhard et al.). Nepal is a country with widespread iodine deficiency up to 13.52% in terms of iodine deficiency. The high incidence of thyroid disorders found in this study may be due to the high incidence of iodine deficiency in this country.

In this study, the incidence of hypothyroidism in women with hyperprolactinemia was 51.1%. In the hypothyroid state, there is a compensatory increase in TRH secretion, which is a potent prolactin-releasing factor, which leads to increased prolactin secretion. In addition, there is no negative feedback due to low thyroid hormone levels in the serum, which can lead to the proliferation and overgrowth of thyroid hormones and pituitary gland lactotrophs and cause an increase in TSH and prolactin levels. Other mechanisms of this prolactin increase may reduce the secretion of some prolactin inhibiting agents, increased pituitary sensitivity to TRH tonic secretion, TSH overgrowth, and prolactin producing cells. Finally, analysis of the ROC curve comparing TSH and prolactin levels using data from this study showed that there is a greater possibility of thyroid dysfunction (especially hypothyroidism) with hyperprolactinemia at prolactin levels above 22.5 ng / ml. One of the disadvantages of this study was that it only showed a measure of the relationship between primary infertility and thyroid disorders and hyperprolactinemia. It takes more work with large samples to create a causal relationship. In this study, the sample size was small, but instead of a set of exclusion criteria that excluded all other causes of infertility, such as the male factor and anatomical abnormalities that interfere with fertilization and implantation, there were representatives of women with infertility. For hormonal reasons that give more reliable results for infertility for hormonal reasons.

CONCLUSION:

Among women with primary infertility, they increased the level of 2/3 prolactin, and almost half have thyroid dysfunction. About half of all patients with hyperprolactinaemia increased TSH levels. From the ROC curve analysis it can be concluded that a higher probability of thyroid dysfunction is associated with hyperprolactinemia. The high incidence of hyperprolactinemia and thyroid disorders in primary cases of infertility emphasizes that all women undergoing infertility tests must undergo thyroid function tests and estimate serum prolactin levels. This should be done as the first line of infertility control instead of going directly to more expensive and invasive procedures. The results emphasize that serum TSH should be predicted in cases with high prolactin to detect hypothyroidism, since the incidence of hypothyroidism is higher in cases of hyperprolactinemia.

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