

## Correlation of serum thyroid stimulating hormone and prolactin in female infertility – a case control study

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### Abstract

**Background:** Thyroid dysfunction and high prolactin levels can affect fertility due to anovulatory cycles, luteal phase defects and sex hormone imbalance. The study was designed to evaluate the status of Thyroid stimulating hormone (TSH) and prolactin in female infertility after exclusion of tubal factor and male factor infertility, and to determine the degree of association of TSH with prolactin in cases of infertility.

**Material & Methods:** The study design was a randomized case control study conducted at Rohilkhand Medical College & Hospital, Bareilly, U.P. The study subjects included 50 infertile and 50 normal fertile women in the age group of 20- 40 years attending Gynaecology OPD during one year study period. The TSH and prolactin hormones were assayed using Enhanced Chemiluminescence Immunoassay and Enzyme Linked Immunosorbent Assay. Student's t-test, Analysis of variance and Pearson's correlation were used to analyze the data, with the significant p-level set at <0.05.

**Results:** We found significantly higher mean TSH and prolactin levels in infertile females when compared with the normal fertile females. The mean TSH values were significantly higher in both primary and secondary infertility cases whereas mean prolactin level was significantly increased in primary infertility cases only. TSH and prolactin levels showed significant positive correlation in both primary and secondary infertility cases.

**Conclusion:** There is a greater propensity for thyroid dysfunction and a higher prevalence of hyperprolactinemia in infertile women than the fertile ones and therefore, estimation of thyroid profile and prolactin should be included in the workup for infertile women.

**Keywords:** Infertility, Thyroid stimulating hormones, Prolactin, Hypothyroidism, Hyperprolactinemia

### Introduction

Human infertility is a major health problem worldwide having its impact on the social, psychological, economical and sexual life of a couple. A couple is said to be infertile when they are not able to conceive within one year of their marriage in spite of regular and unprotected intercourse.<sup>(1)</sup> It could be primary, when a couple has never conceived within the specified period or secondary, when a couple had achieved a pregnancy despite of its outcome.<sup>(2)</sup> There are multiple factors that can lead to the infertility. But it has been seen that among all the cases of infertility, approximately 40% are due to some factors in female, 30% are due to male factors while remaining 30% are due to problems in both partners or unidentified factors.<sup>(3)</sup> Female factors leading to infertility can be broadly categorized into ovulatory disorders, tubal factors and congenital abnormalities. Ovulatory dysfunction is due to many reasons including polycystic ovarian disease and other hormonal imbalance. Ovulation in females is coordinated and regulated by functionally intact hypothalamic-pituitary-ovarian axis by various hormones including follicle stimulating hormone, luteinizing hormone, prolactin (PRL) and thyroid hormones.

Thyroid hormones act synergistically with FSH and LH on ovary to secrete and maintain the normal level of estrogen and progesterone in a menstrual cycle. Anovulatory cycles with decreased fecundity and

consequently infertility have been found to be associated with thyroid dysfunction.<sup>(4,5)</sup> Similarly, high level of prolactin hormone can inhibit follicular estradiol production and gonadotropin cyclicity leading to anovulation.<sup>(6)</sup> It has been seen that estrogen and thyrotropin releasing hormone (TRH) are positive modulators of prolactin leading to its increased secretion and action whereas dopamine is a negative modulator of prolactin secretion.<sup>(7)</sup>

High level of thyroid stimulating hormone (TSH) is found associated with increased prolactin secretion that can lead to ovulatory dysfunction.<sup>(8)</sup> Thyroid hormones help to maintain the normal serum level of progesterone and estradiol essential for normal reproductive function. Therefore, isolated thyroid dysfunction can also cause infertility.<sup>(5)</sup>

### Aim & Objectives

The aim of the study was to evaluate and compare the status of thyroid stimulating hormone (TSH) and serum prolactin (PRL) in age matched infertile females with normal fertile females in the Rohilkhand region of Uttar Pradesh, and to find out any correlation between serum TSH and prolactin in the cases of infertility.

### Material & Methods

The randomized case control study was conducted in the department of Obstetrics & Gynaecology in collaboration with Biochemistry department at

Rohilkhand Medical College & Hospital, Bareilly, U. P., India. Single blind randomization was done using random number table. The study was conducted after getting ethical committee clearance from the institute. Informed, written and understood consent of the participants were taken. The cases included 50 infertile women of reproductive age group (20-40 years) attending the gynecology infertility OPD who were selected over a period of one year (April 2015 to March 2016). Infertile women having tubular blockage, pelvic inflammatory disease, endometriosis and with genital tuberculosis, those already on treatment for thyroid disorders or hyperprolactinemia or cases with abnormality in husband's semen analysis were excluded from the study. Fifty healthy fertile females in similar age group were enrolled as controls. The detailed history and examination of subjects were recorded in a pre-designed data collection sheet.

For serum TSH & prolactin estimation, the morning venous sample was taken and blood was allowed to clot for 30 minutes. Serum was separated using REMI centrifuge and the specimen was stored at 2-8°C for a short time (maximum two days). Quantitative estimation of TSH in the serum was done by Enhanced Chemiluminescence Immunoassay (ECLIA) using the commercial kit and system of Vitros Immunodiagnostic by Orthoclinical Diagnostics, High Wycombe, UK. Serum prolactin estimation was done by Enzyme linked Immunosorbent Assay (ELISA) using the commercial kit and system of Erba diagnostics Mannheim, Germany. Results of TSH and prolactin were collected and recorded in the data sheet. Normal values of serum TSH and prolactin were taken as given in the kit, that were 0.467 - 4.68 µIU/mL and 1.2 - 19.5 ng/mL respectively. **Statistical analysis:** Descriptive statistical analysis was used to study the characteristics of the infertile and fertile women. Means were compared using independent sample t-test, one way analysis of variance (ANOVA) and Tukey's (HSD) post-hoc test whichever was applicable. Pearson correlation of coefficient was used to see the correlation between PRL and TSH levels in the cases of infertility. A two-tailed, at minimum 95% confidence intervals & p value <0.05 was considered

significant. The data was analyzed using Microsoft excel 2007 and statistical package for social science (SPSS) version 17 (IBM, Chicago, USA).

## Results

The current study was designed to compare the values of serum TSH & Prolactin between infertile and fertile females as well as to correlate TSH & Prolactin level in infertile females. The study population was divided into two groups on the basis of fertility i.e. Group I infertile females as cases, Group II normal healthy fertile females as controls. Cases were again subdivided into 2 subgroups of primary and secondary infertile females. Out of 50 infertile subjects, 33 (66%) had primary infertility and 17 (34%) secondary infertility. Most of the women were found to be in the age group of 22-30 years in both the groups. We noted mean age of infertility cases was significantly lower than that of controls. (Table 1)

We noted most of the infertile females (60%) and controls (96%) were euthyroid having serum TSH values within normal range. The serum TSH was found to be higher in 19% cases while only in 4% of controls. Only 2% of cases had lower TSH values than normal range that too found only in the cases. Hyperprolactinemia was noted in 24% of cases but not in controls. The means of serum TSH and prolactin were compared between cases and controls as depicted in Table 1. Further subgroups of the cases were compared with the controls separately as in the Table 2. We found significantly higher TSH and PRL levels in the infertile females when compared with the normal fertile females. Similarly serum TSH was found to be higher in both primary and secondary infertile females but it was only significant in primary infertility cases when compared with the controls. On the contrary, mean serum prolactin level was found to be significantly higher, though in the normal range, in both the primary and secondary infertility cases than that of controls. Correlation of TSH and PRL was studied in the infertility cases and a significant positive correlation was found. (Table 3, Fig. 1)

**Table 1: Comparison of serum TSH & PRL in cases and controls**

Parameters	Cases (n = 50)		Controls (n = 50)		p-value
	Mean ± S.D.	Range	Mean ± S.D.	Range	
Age (years)	27.08 ± 4.49	20 - 40	30.76 ± 4.90	23 - 40	0.00*
TSH (µIU/mL)	05.14 ± 9.95	0.16 - 22.05	02.45 ± 1.40	0.58 - 7.09	0.00*
PRL (ng/mL)	15.41 ± 9.95	0.24 - 44.34	08.05 ± 4.61	2.40 - 22.75	0.00*

\*p-value<0.05 was considered significant

**Table 2: Comparison of serum TSH & PRL in primary and secondary infertility cases with control**

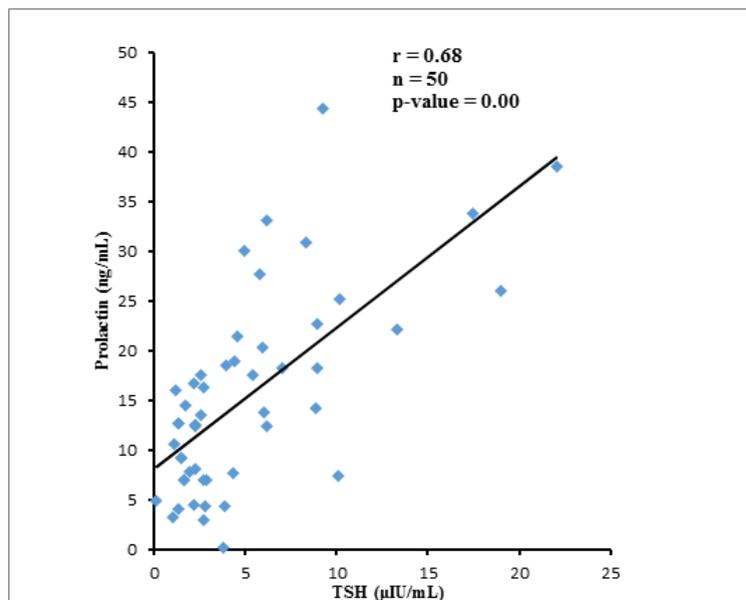
Parameters	Primary Infertility (n = 33)	Secondary Infertility (n = 17)	Control (n = 50)
TSH (µIU/mL)	05.59 ± 4.63**	04.26 ± 4.99	02.45 ± 1.40
PRL (ng/mL)	16.34 ± 8.86**	13.59 ± 11.87*	08.05 ± 4.61

\*p-value&lt;0.05 (0.03)

\*\*p-value&lt;0.01 (0.00)

**Table 3: Correlation between serum TSH & Prolactin in cases of infertility (n = 50)**

Parameters	Mean $\pm$ S.D	Correlation of Coefficient (r value)	p-value
TSH ( $\mu$ IU/mL)	05.14 $\pm$ 4.74	0.68	0.00
PRL (ng/mL)	15.41 $\pm$ 9.95		

**Fig. 1: Correlation plot of TSH against prolactin in infertility cases**

## Discussion

Thyroid hormones secreted by thyroid gland as well as prolactin hormone secreted by anterior pituitary have a major implication on the fertility of a female. Though in our study, majority of infertile and fertile women had serum TSH and serum prolactin within normal range. This finding is in accordance with that inferred in the study of Goswami *et al.*<sup>(9)</sup> But we found higher occurrence of significantly increased serum TSH and prolactin values in infertile women when compared to control group. Other workers in the field have also supported our findings.<sup>(10-13)</sup> Thyroid dysfunction is one of major causes of reproductive disorders including menstrual irregularities, abnormal sexual development and infertility.<sup>(14,15)</sup> Thyroid hormones along with the FSH and LH have synergistic action at granulosa cell and thus have a stimulatory effect on its growth as well as on the secretion of steroid hormones from ovary that are responsible for normal reproductive function.<sup>(5)</sup>

Increased serum prolactin level has also been implicated to affect fertility potential by suppressing hypothalamic-pituitary-gonadal axis and gonadotropin releasing hormone (GnRH) pulsatility. Hyperprolactinemia interferes with the secretion and action of gonadotropins at growing follicles in the ovary thus impairing gonadal steroid secretion which further affects positive feedback on gonadotropins leading to

follicular immaturity and consequently infertility with anovulation.<sup>(6)</sup>

When we analyzed the values of serum TSH and PRL in the primary & secondary infertility cases separately, we noted significantly higher values of both the parameters in primary infertility cases while in secondary infertility cases, only prolactin level was found significantly increased when it was compared with the levels in fertile females. These findings were in conformity with those of Kumkum *et al.*<sup>(13)</sup> This observation inferred more prevalence of hormonal imbalance in primary infertility group than secondary infertility group. This could be due to effect of many other factors involved in secondary infertility which could not be easily revealed and diagnosed.

A significant positive correlation ( $r = 0.68$ ,  $p < 0.05$ ) was observed between TSH and prolactin levels in both primary and secondary infertility cases. Similar type of positive significant correlation was also observed by other researchers in their studies.<sup>(7,9,10,16)</sup> Prolactin level in serum is regulated by both hypothalamus and pituitary. Dopamine, a neurotransmitter and progesterone inhibits its secretion and synthesis respectively under normal physiological condition. In case of hypothyroidism, low serum level of thyroxine ( $T_4$ ) causes decreased negative feedback on the hypothalamo-pituitary axis leading to increased TRH

secretion which further stimulates thyrotrophs and lactotrophs secretion from the pituitary, thereby increasing the level of both TSH and prolactin.<sup>(17)</sup> Chernova et al (1994)<sup>(18)</sup> studied the origin of hyperprolactinemia in subjects of primary hypothyroidism by using a dopaminergic blocker, the metoclopramide. They studied 20 women presenting with primary hypothyroidism and normal prolactin levels as case and 10 women with primary hypothyroidism and hyperprolactinemia as control. Prolactin secretion observed in metoclopramide test in cases was markedly increased as compared to the control group. The study concluded that hyperprolactinemia in patients with hypothyroidism was possibly by disturbed dopaminergic regulation.<sup>(18)</sup>

Kumkum et al (2006)<sup>(13)</sup> also studied the correlation between TSH and prolactin in 111 patients of infertility and noted 25.5% prevalence of hypothyroidism in hyperprolactinemia. In our study we found the prevalence of 69.23% in infertility cases considering hypothyroidism as serum TSH value > 6.00  $\mu$ U/mL. Vice versa, we found prevalence of hyperprolactinemia to be 60% in the cases of hypothyroidism. These findings in our study were strongly supported with those of Goswami et al (2009),<sup>(9)</sup> who also reported 46.1% infertile women with hypothyroidism developing hyperprolactinemia. In another recent study conducted by Lal et al (2016),<sup>(10)</sup> 40.7% of infertile women with hypothyroidism were found exhibiting hyperprolactinemia.

Increased TRH production in the cases of hypothyroidism promotes hyperprolactinemia which in turn affects pulsatile secretion of GnRH. This leads to delay in LH response leading to abnormal follicular development and anovulation. Hypothyroidism also alters the peripheral metabolism of estrogen by decreasing sex hormone binding globulin production. This may be another pathway by which it may have resulted in abnormal feedback at pituitary level impairing the fertility.<sup>(5)</sup>

## Conclusion

In the present study, there was high prevalence of increased TSH levels in the infertile females especially in the primary infertility. We also noted a strong positive correlation between serum TSH and prolactin in infertile women. Thyroid dysfunction and altered prolactin levels may lead to ovulatory dysfunction resulting in infertility. Thus, infertility work up of a woman requires a multidimensional diagnostic approach with hormonal assay including thyroid hormones especially TSH and prolactin levels, regardless of their menstrual cycle pattern at the time of first consultation.

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## Conflict of Interest

We, the authors deny any conflicts of interest related to this study.

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