Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Evaluation of Correlation of Serum TSH and prolactin in Female Infertility: A Teaching Hospital Based Study.

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Received: February 2017
Accepted: February 2017

ABSTRACT

Background: 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. 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. There are multiple factors that can lead to the infertility. **Methods:** The cases included 46 infertile women of reproductive age group (21-42 years) attending the gynecology infertility OPD who were selected over a period of one year. 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. The detailed history and examination of subjects were recorded in a pre-designed data collection sheet. Forty six healthy fertile females in similar age group were enrolled as controls. **Result:** Out of 46 infertile subjects, 30 (65.2 %) had primary infertility and 16 (34.8 %) secondary infertility. Most of the women were found to be in the age group of 25–34 years in both the groups. We noted mean age of infertility cases was significantly lower than that of controls. 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. **Conclusion:** Significant positive correlation between serum TSH and prolactin in infertile women.

Keywords: TSH, PRL and Infertility.

INTRODUCTION

The hormonal disorders of female reproductive system is comprised of a number of problems resulting from aberrant dysfunction of hypothalamic-pituitary-ovarian axis. These relatively common disorders often lead to infertility. Difficulty to conceive or subfertility constitutes a major psychological burden. Proper evaluation of these disorders involves a multidimensional diagnostic approach, with a pivotal contribution from clinical laboratories.[1] 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.[2] 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.[3] 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.[4] 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. Measurement of prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH), has been considered an important component of infertility work up in women.[5] Thyroid dysfunctions interfere with numerous aspects of reproduction and pregnancy. Several articles have highlighted the association of hyperthyroidism or hypothyroidism with menstrual disturbance,

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anovulatory cycles, decreased fecundity and increased morbidity during pregnancy.[6-8] The increased prevalence of upper normal limit of serum TSH and raised anti-thyroperoxidase antibody titer indicate relatively more frequent occurrence of compensated thyroid function in infertile women than normal women of reproductive age. This necessitates considering such cases a subgroup of women in which all aspects of pituitary-thyroid axis should be thoroughly investtigated than merely do with TSH testing.[9] Despite normal TSH and free thyroxin (FT4) concentrations, some patients may exhibit the clinical picture of hypothyroidism. Treating such thyroid dysfunction with low dose thyroxin slightly increases FT4 levels leading to inhibition of TSH secretion within normal range, resulting in subjective improvement in health status, normalization of menstrual abnormalities and restoration of normal fertility.[10] Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation.[11,12] This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhea, oligomenorrhea, anovulation, inadequate corpus luteal phase and galactorrhea.[13,14] However many infertile women present with normal menses despite a raised serum prolactin level. Pituitary hormones such as TSH, prolactin or growth hormone may act synergistically with FSH and LH to enhance the entry of non-growing follicles into the growth phase. Morphological changes observed in the follicles in hypothyroidism can be a consequence of higher prolactin production that may block both secretion and action of gonadotropins.[15] Adequate thyroid supplementation restores prolactin levels as well and normalizes ovulatory function.[16] Even in the absence of hyperprolactinemia, hypothyroidism itself may contribute to infertility since thyroid hormones may be necessary for the maximum production of both estradiol and progesterone.[17] High level of thyroid stimulating hormone (TSH) is found associated with increased prolactin secretion that can lead to ovulatory dysfunction.[18] 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.[19] The aim of the present study was to evaluate the Correlation of Serum TSH and prolactin in female infertility.

MATERIALS AND METHODS

This present study was conducted in the Department of Obstetrics and Gynecology in collaboration with Biochemistry department at Rama Medical College Hospital and Research Centre, Hapur, Ghaziabad, UP during the period November, 2015 to October, 2016. 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 46 infertile women of reproductive age group (21-42 years) attending the gynecology infertility OPD who were selected over a period of one year. 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. The detailed history and examination of subjects were recorded in a pre-designed data collection sheet. Forty six healthy fertile females in similar age group were enrolled as controls.

Biochemical Analysis:

Fasting 5 ml venous blood samples were collected from all participants in there early follicular phase of menstrual cycle i.e. between days 3rd to 5th in plane bulbs. Unique ID was given to all participants and same ID was mentioned on sample bulb to hidden identity of patients. Serum was separated after 1 hour by centrifugation at 3000 rpm for 10 minutes, and was tested for following parameters by chemiluminance technology.

a. Serum TSH (Reference range:0.5-5 microIU/ml) and
b. Serum Prolactin (Reference range:2-29 microIU/ml)

Statistical analysis was done using the unpaired T-test and Pearson correlation of coefficient was used to see the correlation between PRL and TSH levels in the cases of infertility.

RESULTS & DISCUSSION

Table 1: Shows the mean and srandard deviation of serum TSH & PRL

Variables	Infertile as cases (N= 46)		Fertile as Controls (N = 46)	
	Range	Mean ± S.D.	Range	Mean ± S.D.
Age (years) **	21 - 42	29.24 ± 5.21	22 - 41	26.34 ± 4.23
Thyroid Stimulating Hormones-TSH (µIU/mL)*	0.15 – 22.10	07.12 ± 3.25	0.56 – 7.11	02.25 ± 1.21
Prolactin-PRL (ng/mL)*	0.22 – 44.24	17.32 ± 8.52	2.36 – 23.14	06.71 ± 4.43

(*Statistically significant; p<0.05; **Statistically not significant)

This case-controls study was conducted in the Department of Obstetrics and Gynecology, Rama Medical College Hospital and Research Centre, Hapur, Ghaziabad, Uttar Pradesh. The current study was designed to compare the values of serum TSH & Prolactin between infertile and fertile females and its correlation with TSH & Prolactin in infertile females. The study population was divided into two groups on the basis of fertility i.e. infertile females as cases and normal healthy fertile females as controls. Cases were again subdivided into 2 categories i.e.;

primary and secondary infertile females. Out of 46 infertile subjects, 30 (65.2 %) had primary infertility and 16 (34.8 %) secondary infertility. Most of the women were found to be in the age group of 25–34 years in both the groups. We noted mean age of infertility cases was significantly lower than that of controls in [Table 1].

[Table 2 & Figure 1] Shows the 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. [Table 3] Shows the Correlation of TSH and PRL was studied in the infertility cases and a significant positive correlation was found.

Table 2: Shows the mean and srandard deviation level of serum TSH & PRL in primary and secondary infertility

Parameters	Primary Infertility (n = 30)	Secondary Infertility (n = 16)	Control (n = 46)
TSH (μIU/mL)	6.15 ± 3.41**	4.05± 2.32	2.16 ± 1.04
PRL (ng/mL)	17.26 ± 7.61**	14.28 ± 10.29*	7.42 ± 3.26

(*Statistically significant; p<0.05; **Statistically not significant)

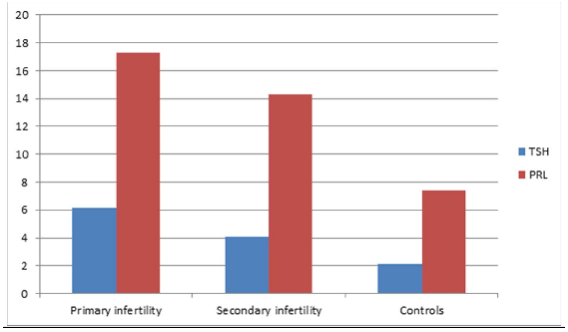

Figure 1: Shows the mean level of serum TSH & PRL in primary and secondary infertility.

Table 3: Correlation between serum TSH & Prolactin in cases of infertility

Variables	Correlation Coefficient (r value)
Correlation between serum TSH & Prolactin	+0.52

(Statistically significant; p<0.05)

Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome. Data on the relationship between thyroid disorders and infertility remain scarce and the association with a particular cause of infertility has not been thoroughly analyzed.[20] The increase in prolactin secretion can be physiological e.g. during pregnancy and lactation or pathological due to hypothalamic and pituitary diseases, or it can be iatrogenic. Hyperprolactinemia induces suppression of the hypothalamic-pituitary-gonadal axis and resistance of the ovary to gonadotropin action, which results in amenorrhea and lack of ovulation.[21] 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.[13] 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.[14-17] Thyroid dysfunction is one of major causes of reproductive disorders including menstrual irregularities, abnormal sexual development and infertility.[22,15] 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.[8] Increased serum prolactin level has also been implicated to affect fertility potential by suppressing hypothalamic-pituitary-gonadal axis and gonadotropin releasing hormone (GnRH) pulsatility. Hperprolactinemia 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.[9] 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.[17] 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 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.[10,13,14,24] 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 causes decreased negative feedback on the hypothalamo-pitutary 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.[25] Chernova et al (1994),[26] studied the origin of hyperprolactinemia in subjects of primary hypothyroidism by using a dopaminergic blocker, the metaclopramide. 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 metaclopramide 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.[26] Kumkum et al (2006),[17] 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 68.04% in infertility cases considering hypothyroidism as serum TSH value > 6.00 µIU/mL. Vice versa, we found prevalence of hyperprolactinemia to be 59% in the cases of hypothyroidism. These findings in our study were strongly supported with those of Goswami et al (2009),[13] who also reported 46.1% infertile women with hypothyroidism developing hyperprolactinemia. In another recent study conducted by Lal et al (2016),[14] 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. For these reasons, TSH and prolactin are commonly-ordered clinical tests in evaluating infertile women.

CONCLUSION

Theses findings suggest that, the high prevalence of increased TSH levels in the infertile females especially in the primary infertility. We also noted significant positive correlation between serum TSH and prolactin in infertile women. Thyroid dysfunction and altered prolactin levels may lead to ovulatory dysfunction resulting in infertility. This is also associated with hyper prolactinemia and these patients are commonly associated with ovulatory failure. Hence, assessment of serum TSH and prolactin levels are mandatory in the work up of all infertile women, especially those presenting with menstrual irregularities.

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How to cite this article: Amar S. Evaluation of Correlation of Serum TSH and prolactin in Female Infertility: A Teaching Hospital Based Study. Ann. Int. Med. Den. Res. 2017; 3(2):OG07-OG11.

Source of Support: Nil, **Conflict of Interest:** None declared