

## Correlation of Prolactin and Thyroid Hormone Concentration with Menstrual Patterns in Infertile Women

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### Abstract

**Introduction:** The increased prevalence of upper normal limit of TSH and raised anti-thyroperoxidase antibody titer indicate, relatively more frequent occurrence of compensated thyroid function in infertile women. This finding necessitates considering such cases for a thorough investigation of pituitary-thyroid axis. In addition, as some patients may exhibit the clinical picture of hypothyroidism despite normal TSH and free thyroxin (FT4) concentrations, this hospital-based study was undertaken to review the impact of thyroid status on the menstrual function and fertility of the subjects.

**Materials and Methods:** In this study, we investigated 160 women with primary infertility who attended the Biochemistry department, Maulana Azad Medical College (MAMC), New Delhi for hormonal evaluations. Eighty fertile women with similar age and socioeconomic status were enrolled as the controls. The association between thyroid dysfunction and levels of serum prolactin, LH and FSH as their menstrual status were reviewed.

**Results:** The majority of the infertile and fertile women were euthyroid. In infertile group, the crude prevalence of hypothyroidism was slightly higher in the infertile group in comparison with that of the general population. There was a positive correlation between serum TSH and prolactin levels in the infertile subjects. Menstrual disorders (mainly oligomenorrhea), were reported by about 60% of the infertile women. Hyperprolactinemia was depicted in 41% of the infertile women while it was only 15% in the control group. The infertile women with hypothyroidism had significantly higher prolactin levels when compared to the subjects with hyper- or euthyroidism. There was a significant association between abnormal menstrual patterns and anovulatory cycles, as observed on endometrial examination of infertile subjects with raised serum prolactin levels.

**Conclusions:** There is a greater propensity for thyroid disorder in infertile women than the fertile ones. There is also a higher prevalence of hyperprolactinemia in infertile patients.

**Keywords:** Anovulatory cycles, Hyperprolactinemia, Infertility, Menstrual disturbances.

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**H**ormonal 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 diag-

### Introduction

nostic approach, with a pivotal contribution from clinical laboratories (1).

Measurement of prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH), has been considered an important component of infertility work up in women (2). Thyroid dysfunctions interfere with numerous aspects of reproduction and pregnancy. Several articles have

highlighted the association of hyperthyroidism or hypothyroidism with menstrual disturbance, anovulatory cycles, decreased fecundity and increased morbidity during pregnancy (3,4,5). 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 investigated than merely do with TSH testing (6). 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 (7).

Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation (3,8). This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhea, oligomenorrhea, anovulation, inadequate corpus luteal phase and galactorrhea (9,10). 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 (7). 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 (11). Adequate thyroid supplementation restores prolactin levels as well and normalizes ovulatory function (12). 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 (13).

In areas with endemic goiter, the major contributor of thyroid dysfunction is iodine deficiency. Infertility associated with thyroid dysfunction in these areas is not uncommon (14). The

prevalence of thyroid dysfunction among the infertile females in Delhi and its suburban areas, which is considered as a non-endemic zone for iodine deficiency, had not been studied prior to this research.

The aims of the study were to find the prevalence of thyroid disorders in female infertility after exclusion of tubal factor and male factor infertility in Delhi and suburbs from a hospital-based study and to investigate the impact of the thyroid status on serum prolactin, FSH and LH of the third day of menstrual cycle.

### **Materials and Methods**

The cases consisted 160 female subjects who were suffering from primary infertility and had been referred the Department of Biochemistry of Maulana Azad Medical College, New Delhi for hormonal evaluations. The cases were selected over a period of six months. The inclusion criteria for the selection of cases were diagnosis of primary infertility, age between 20-40 years and duration of marriage more than one year. The exclusion criteria that were adopted during case selection were male factor infertility and amongst the female factors were tubal factor, any congenital anomaly of the urogenital tract, or any obvious organic lesion. Any history of thyroid disease or previous thyroid surgery or being on thyroid medications were also amounted to exclusion for the study.

The protocol for infertility work up in the women included: a detailed medical history, a gynecological examination, a premenstrual endometrial sampling, an ultrasonography, a hormonal profile (TSH, FT4, FT3, prolactin, FSH and LH), screening for infectious diseases and whenever indicated, hysterosalpingography and/or laparoscopy. Eighty healthy fertile female employees of Lok Nayak hospital, New Delhi with similar age range and socioeconomic status were enrolled as controls. The participants were enrolled after signing on informed consent.

Five milliliters of fasting venous sample obtained in the morning of day three of menstrual cycle for serum biochemical analysis. Serum was separated and stored for further analysis. All the hormones were estimated using electrochemiluminescence kits of TSH, FT3, FT4, prolactin, LH and FSH (Roche diagnostics; Mannheim,

Germany) and estimated on Elecsys 2010 (Roche Healthcare, Basel, Switzerland). Assay reliability was determined by the use of commercially derived control sera of low and high concentrations.

The normal range of serum prolactin and TSH were 2-25ng/ml and 0.5-4.7mIU/L respectively. Women with serum prolactin levels >100ng/ml were advised to undergo CT scan or MRI to rule out any pituitary pathology.

As per the serum TSH profile the cases, as well as the controls, were divided into three groups:

I Euthyroidism was present when the value of TSH was within the normal range.

II Hyperthyroidism was diagnosed if serum TSH was <0.5mIU/L.

III Hypothyroidism was diagnosed if serum TSH was >4.7mIU/L.

Patients with subclinical hyperthyroid as well as those with hypothyroidism were not included in the study.

Statistical analysis was done by using SPSS software, version 12 (SPSS Inc, Illinois, USA) through Chi-Square test and Mann Whitney U test calculations. Spearman's correlation was used to look for association between different variables in the study group. A p-value <0.05 was considered statistically significant.

## Results

Thyroid function status in the study population is depicted in table 1. Most of the control (86%) and infertile women (87%) were euthyroid. The prevalence of hyperthyroidism in the cases and the controls were 5% and 9%, respectively. Hypothyroidism was seen in 8% of the infertile subjects whereas in the control group it was found

to be 5%. The crude prevalence of hypothyroidism was slightly higher when compared to hyperthyroidism in the infertile group.

The mean serum levels of TSH, FT4, FT3, LH, FSH and prolactin in the study group are depicted in table 1. Significantly higher serum TSH levels were noted in the infertile cases with euthyroidism ( $p<0.01$ ) and hypothyroidism ( $p<0.001$ ) when their distributions were compared to their respective control groups. The rise in serum FT4 and FT3 in the infertile group with hyperthyroidism was found to be significantly higher as compared to the control group with hyperthyroidism ( $p<0.001$ ). Serum FT4 value was significantly lower ( $p<0.01$ ) in the infertile group with hypothyroidism when compared to the control group with hypothyroidism.

Hyperprolactinemia was depicted in 41% of the infertile women while it was the case in only 15% in the control group. The mean serum prolactin concentration in the infertile cases with euthyroidism was significantly higher ( $p<0.001$ ) than the control group with euthyroidism. The infertile women with hypothyroidism had significantly higher prolactin levels than the other three groups (the controls and the infertile subjects with euthyroidism and hyperthyroidism) ( $p<0.001$ ).

The serum LH and FSH levels in the infertile patients with hyperthyroidism were found to be significantly higher than the control group with hyperthyroidism ( $p<0.001$  and  $p<0.05$ , respectively).

Menstrual disturbances observed in the control and infertile groups were 18.7% and 61.2%, respectively (Table 2). The majority of the cases (82.6%) as well as the controls (66.7%) who

**Table 1.** Hormonal status in the whole study groups (values are expressed in mean  $\pm$ SD)

	CASES (n=160)			CONTROLS (n=80)		
	Euthyroid (n=139)	Hyperthyroid (n=8)	Hypothyroid (n=13)	Euthyroid (n=69)	Hyperthyroid (n=7)	Hypothyroid (n=4)
TSH (mIU/L)	3.3 $\pm$ 1.2**	0.16 $\pm$ 0.06	27.8 $\pm$ 9.16***	1.4 $\pm$ 0.8	0.15 $\pm$ 0.1	7.5 $\pm$ 2.1
FT4 (pmol/L)	18.6 $\pm$ 3.4	31.7 $\pm$ 10.9***	7.6 $\pm$ 2.2**	17.1 $\pm$ 3.1	17.5 $\pm$ 4.8	15.8 $\pm$ 2.4
FT3 (pmol/L)	4.6 $\pm$ 1.3	8.5 $\pm$ 1.4***	1.9 $\pm$ 0.7	4.6 $\pm$ 1.1	5.2 $\pm$ 1.6	3.7 $\pm$ 0.8
LH (mIU/ml)	5.8 $\pm$ 2.9	12.9 $\pm$ 4.1***	5.6 $\pm$ 2.3	5.9 $\pm$ 2.1	5.0 $\pm$ 2.2	6.5 $\pm$ 2.5
FSH (mIU/ml)	6.2 $\pm$ 2.1	10.0 $\pm$ 5.2*	7.2 $\pm$ 3.9	5.9 $\pm$ 2.1	6.4 $\pm$ 2.1	4.5 $\pm$ 1.3
Prolactin (ng/ml)	40.1 $\pm$ 18.9***	18.5 $\pm$ 8.7**	84.6 $\pm$ 27.9	17.8 $\pm$ 6.9	9.4 $\pm$ 2.4	38.2 $\pm$ 12.6

\* $p<0.05$ , \*\* $p<0.01$  and \*\*\* $p<0.001$  in comparing the distributions (Mann-Whitney test) to the respective group in controls.

**Table 2.** Distribution of menstrual irregularities and anovulatory cycles in the controls and the infertile group

	Menstrual Dysfunction	Anovulatory Cycles
Cases	98 (61%)	87 (54%)
Controls	15 (19%)	3(3%)
Total	113 (47%)	90 (37%)

P<0.001 by Chi Square Test

presented with menstrual disturbances, had oligomenorrhea. Fifty percent of the subjects with hypothyroidism had menstrual irregularities, presented with amenorrhea.

Among the infertile women, 54 % showed non-secretory endometrium in premenstrual endometrial samples suggestive of the presence of an anovulatory cycle.

Serum TSH levels were found to be positively correlated with prolactin levels in the cases ( $r=0.4$ ,  $p=0.01$ ).

### Discussion

In this study, the majority of infertile as well as fertile women were euthyroid. However, the distribution of thyroid dysfunction in the study group was somehow different – hyperthyroidism being more prevalent in the controls whereas hypothyroidism was more prevalent in the infertile group. Elahi *et al.* (6) also depicted such pattern of thyroid dysfunction. Some investigators had claimed an association between mild iodine deficiency with hyperthyroidism and less frequently with hypothyroidism in the population (15,16,17). A relatively higher occurrence of hypothyroidism in infertile women, when compared to the control group in this study, reflects the tendency of infertile patients towards thyroid insufficiency or the vice versa.

The prevalence of hypothyroidism in women of reproductive age (20-40 years) varies between 2% to 4% (18,19). Relatively higher crude prevalence rate of hypothyroidism (8%) in the infertile women found in our study could be due to special referral pattern of the patients who were referred to the hospital based on suspicion of thyroid abnormalities.

A higher occurrence of hyperprolactinemia (41%) was seen in the infertile group as compared to the controls (15%) in this study. This higher propensity of hyperprolactinemia is in agreement

with the findings of Kumkum *et al* (20) who had depicted a prevalence of 46% in their study. As per the study, we observed a greater percentage of infertile patients with hypothyroidism exhibiting hyperprolactinemia (46.1%). Choudhary and Goswami (21) observed hyperprolactinemia in 16.6% and Singh *et al* in 57% of women with hypothyroidism (22). Fifty-eight percent of infertile women with raised serum prolactin levels showed nonsecretory endometrium suggestive of anovulation. Kumkum *et al* (20) showed an incidence of anovulation in hyperprolactinemia patients to be 73%. Prevalence of ovulatory dysfunction, as one of the causes of female infertility, has been variously reported in different studies: 31.4% (22) and 51.4% (9).

Menstrual abnormalities were detected in about 60% of the infertile cases in this study, which is nearly similar to that observed by Kumkum *et al* (20) who had reported the abnormality to be 57.6% in their study. Anovulatory cycles were present in 54% of the cases, which corroborates with the finding of Kumkum *et al* (50%).

Maximum percentage of menstrual abnormality presented by the infertile group was oligomenorrhea (82%) whereas Kumkum *et al* (20) depicted the state to be smaller (50%).

In the study done by Krasses *et al* (24), the prevalence of menstrual irregularities (mainly oligomenorrhea) reached 23% among 171 hypothyroid patients, while being only 8% in 214 controls ( $p<0.05$ ). The authors had shown an association between the severity of menstrual abnormalities and higher serum TSH concentrations. We reported irregular menstrual cycles, mainly amenorrhea, in 31 % of the cases with hypothyroidism. Our study revealed an association between menstrual irregularities with raised serum prolactin levels ( $p<0.001$ ) rather than TSH concentrations. A higher incidence of amenorrhea could be linked to hyperprolactinemia that was seen in the majority of patients with hypothyroidism.

Hyperthyroidism was found in 8% of the infertile patients in the present study. Joshi *et al* (25) evaluated 53 hyperthyroid patients and found 5.8% of them to be infertile. In contrast to hypothyroidism, most women with hyperthyroidism do not have fertility problems, although 25% may have irregular menses (26). Joshi *et al*

found menstrual irregularities in 65% of hyperthyroid women compared to 17% in healthy controls (25). Likewise, our study revealed that 62.5 % of hyperthyroid cases had menstrual disturbances. Krasses *et al* indicated that menstrual disturbances in thyrotoxicosis are 2.5 times more frequent than in the general population (26).

Hyperprolactinemia resulting from longstanding primary hypothyroidism has been implicated in ovulatory dysfunctions ranging from inadequate corpus luteal progesterone secretion when mildly elevated to oligomenorrhea or amenorrhea when circulating prolactin levels are high (27). Amenorrhea occurs in hypothyroidism due to hyperprolactinemia resulting from a defect in the positive feedback of estrogen on LH, and because of LH and FSH suppression. Our study revealed a significant association between abnormal menstrual patterns, as well as anovulatory cycles, with hyperprolactinemia in the infertile group ( $p < 0.001$ ).

For these reasons, TSH and prolactin are commonly-ordered clinical tests in evaluating infertile women.

The main drawback of the present study was the number of participants in the study. Only 80 controls could be included in the study as compared to 160 cases due to the stringent inclusion criteria and non-compliance.

### Conclusion

There was a higher crude prevalence of hypothyroidism and hyperprolactinemia in the infertile women as compared to the fertile ones in the control group. Both hypothyroidism and hyperthyroidism may result in menstrual disorders. Hypothyroidism is commonly associated with hyperprolactinemia and such patients exhibit 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. To avoid the slightest traces of selection bias, the data should be extrapolated to the general population with care, as the study has been a hospital-based one due to the difficulties in recruiting counterparting controls. For a better calculation of the intended prevalence, a population-based study may be conducted.

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