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Case controlled study

Female infertility and its correlation with serum Prolactin and TSH Concentration-An unmatched case control study

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Abstract:
Background:- Infertility represents a common condition nowadays, with important medical, economic and psychological implications. Traditionally, measurement of Prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH) has been considered an important component of infertility workup in women.

Aims: - The study was designed to evaluate the status of thyroid function in female infertility after exclusion of tubal factor and male factor infertility, and to investigate the impact of thyroid status on serum Prolactin.

Method: -In this retrospective case control study, we investigated fifty (50) infertile women in the age range of 20- 40 years attending department of Biochemistry, MMMSR, Mullana (Ambala) for hormonal evaluation from November, 2010 to October, 2011. Fifty (50) fertile women with similar age range were selected as controls. The association between thyroid dysfunction and levels of serum Prolactin was reviewed.

Results: - The majority of infertile and fertile women were euthyroid and there was no significant association between Infertility & TSH (p > 0.05). Hyperprolactinemia was depicted in 32% infertile women. Prevalence of primary infertility was 76% while that of secondary infertility cases was 24%. There was a negative correlation between serum TSH and Prolactin levels in infertile subjects (p < 0.05).

Conclusion: - There was higher prevalence of hyperprolactinemia with normal thyroid function in infertile patients.

Keywords: Thyroid Stimulating Hormone (TSH), Prolactin (PRL), Hyperprolactinemia, Infertility.

Introduction:

Infertility is defined as the inability to conceive after one year of regular intercourse without contraception. There are number of problems associated with hormonal disorders of female reproductive system. All these disturbances result from aberrant dysfunction of hypothalamic-pituitary-ovarian axis. These relatively common disorders often lead to infertility constituting a major psychological burden. Infertility may be primary if participation of either partner does not turn out to be successful in achieving pregnancy or secondary if couple has achieved a pregnancy previously but are having difficulty currently with conception¹². Fertility in men and women is regulated by a series of tightly coordinated and synchronized interactions within the hypothalamic-pituitary-gonad axis. The operational characteristics of the reproductive axis leave little room for error. Reproductive tract structures are also at risk for the development of diseases that render them unfit or compromised in their primary role of reproduction. Disorders at any level of the system may lead to involuntary infertility, which affects approximately 15% to 20% of couples, or approximately 11 million reproductive-age people in the United States³. In India, evidence on the prevalence of infertility is sparse and dated. The WHO’s estimates of primary and secondary infertility in India are 3% and 8%, respectively (WHO 1980, 1984). Data extrapolated from WHO by the Indian Council of Medical Research(ICMR) suggested that approximately 13–19 million couples are likely to be infertile in India at any given time (ICMR and NAMS 2005)⁴. According to standard protocol, infertility evaluation usually identifies different causes, including male infertility (30%), female infertility(35%), the combination of both(20%) and finally unexplained or “idiopathic” infertility (15%)³⁵. Measurement of prolactin and thyroid hormones especially thyroid stimulating hormone (TSH) has been considered an important component of
infertility work up in women[6]. Thyroid dysfunction is known to interfere with several aspects of reproduction and pregnancy. hypothyroidism or hyperthyroidism in females along with subclinical thyroid dysfunction have been found to be associated with anovulatory cycles, decreased fecundity and increased morbidity during pregnancy by number of authors[7-9]. Hyperprolactinemia also adversely affects the fertility potential by impairing pulsatile secretion of GnRH & hence interfering with ovulation[7,10]. It may be seen in menstrual and ovulatory dysfunction like anovulation, amenorrhea and galactorrhoea[11,12]. Pituitary hormones such as TSH, prolactin or growth hormone may act synergistically with follicle stimulating hormone (FSH) and lutenizing hormone (LH) to enhance the entry of non growing follicles into growth phase. Studies have highlighted that even in the absence of hyperprolactinemia, thyroid dysfunction itself may contribute to infertility since thyroid hormones may be necessary for maximum production of both estradiol & progesterone[13]. There has been paucity of data regarding the association between thyroid disorders and Prolactin levels in infertility. So, the aim of the study was to evaluate the status of thyroid function in female infertility in a rural set up of Haryana and to investigate the impact of thyroid status on serum Prolactin levels.

Materials & Methods:
This was a hospital based, retrospective case control study conducted in a rural setting of Haryana. This area is an endemic zone of iodine deficiency in India. The cases consisted of 50 female subjects who were suffering from infertility and had been referred to the department of Biochemistry of MMIMSR, Mullana for hormonal evaluations. The cases were selected over a period of 1 year from November, 2010 to October, 2011. The inclusion criteria for the selection of cases were diagnosis of infertility (both primary & secondary) and age between 20-40 years. The exclusion criteria that were adopted during case selection were male factor infertility and amongst female factors were tubal factor, any congenital anomaly of urogenital tract or any obvious organic lesion. Any history of thyroid disease or previous thyroid surgery or being on medications for thyroid disorders or hyperprolactinemia was also amounted to exclusion for the study. These criteria were laid down after checking the detailed history of subjects recorded. TSH and prolactin levels were 0.28-6.82 μIU/ml and 1.2-19.0ng/ml respectively. These values were used to confirm abnormal cases and then to find association between thyroid dysfunction & Prolactin levels.

Statistical analysis:
For the statistical data analysis, descriptive statistics were used to show the characteristics of the infertile and fertile women. Means were compared using independent ‘t’ test. Pearson/spearman correlation coefficient, whichever was applicable, has been used to see the correlation between infertility, PRL and TSH levels. A two-tailed, at minimum 95% confidence intervals & p value <0.05 has been considered significant. All the data were analysed using Statistical package for social science (SPSS) version 20 (IBM, Chicago, USA).

Results
Data on 50 infertile and 50 fertile women from study population were taken for analysis. The mean age of the cases was 28.30±5.5 years while for control it was 26.80±3.80 years. Mean age of the cases and control was not statistically different to each other (p value = 0.11). Out of the
total 50 infertile women, 76% were suffering from primary infertility while 24% were suffering from secondary infertility. The mean age of the primary infertile women was found less than that of secondary infertile women which was significantly different statistically (27.52±3.71 versus 29.00±5.60 years, p value = 0.04). On studying serum Prolactin levels of 100 subjects, 32% had higher Prolactin levels while 68% had normal levels. Of those who had hyperprolactinemia, 19 (59.37%) women had infertility (either primary or secondary) and 13 (40.63%) were amongst controls (Table 1). The mean prolactin levels in infertile patients were 21.52±17.71 ng/ml against the controls who had mean Prolactin levels of 15.22±9.54 ng/ml (normal = 1.2-19 ng/ml) and both groups are showing statistically significant difference to each other (p value = 0.03) (Table 2). Out of 50 infertile patients, 19 (38%) had higher Prolactin values against 50 controls, out of which 13 (26%) had higher PRL values than normal and none had lower prolactin values in either of these groups (Table 1).

### Table 1. Showing Serum prolactin and TSH levels in infertile patients and fertile subjects

<table>
<thead>
<tr>
<th>INFERTILITY</th>
<th>Infertile Patients (n=50)</th>
<th>Fertile Subjects (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Serum Prolactin (PRL) levels in ng/ml (Normal: 1.2-19 ng/ml)</td>
<td>59.37%</td>
<td>40.63%</td>
</tr>
<tr>
<td>n=100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Serum TSH levels in μIU/ml (Normal: 0.28-6.82 μIU/ml)</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>n=100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean serum TSH levels in infertile patients were 4.9±2.5 μIU /ml against the controls who had mean serum TSH levels of 4.1±2.3 μIU /ml (normal = 0.28-6.82 μIU/ml) and both groups are not statistically significantly different to each other (p value = 0.09) (Table 2). Out of 50 infertile women, 18 (36%) had higher TSH values than normal against 50 controls out of which 14 (28%) had higher TSH values than normal (normal =0.28-6.28 μIU/ml) (Table 1).

### Table 2. Table showing Mean Hormonal Status in Infertile Patients and Fertile Subjects (*p>0.05, **p < 0.05)

<table>
<thead>
<tr>
<th>HORMONE LEVELS</th>
<th>Infertile patients (n=50)</th>
<th>Fertile subjects (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Mean Serum TSH levels in μIU/ml (Normal: 0.28-6.82 μIU/ml)</td>
<td>4.9±2.51</td>
<td>4.1±2.32</td>
</tr>
<tr>
<td>**Mean Serum Prolactin (PRL) levels in ng/ml (Normal: 1.2-19 ng/ml)</td>
<td>21.52±17.71</td>
<td>15.22±9.54</td>
</tr>
</tbody>
</table>

**Correlation between TSH & PRL levels:**

The Pearson’s correlation coefficient was calculated for serum TSH and PRL in both the study groups (infertile women & controls). In infertile women (both primary and secondary), the result indicated that prolactin levels are negatively correlated with corresponding TSH levels (r = -0.2, p < 0.05) (Figure 1). PRL also showed weak positive correlation with infertility (r=0.12, p<0.05). Similarly, TSH levels was positively correlated with infertility but this correlation was found statistically non-significant (r=0.34, p>0.05). In controls, there was no significant correlation between TSH and prolactin levels (r>0.05).
Discussion:
Thyroid hormones have profound effects on reproduction and pregnancy. In this study, the majority of infertile and fertile (controls) women had serum TSH & serum PRL level within normal range. This is in concordance with study of Binita Goswamy et al.\[14\]. The deranged PRL levels were more in infertile patients (59.37%) as compared to fertile controls (40.63%). In infertile patients with deranged TSH, 36% had higher TSH levels which were more as compared to fertile women in whom 28% had higher TSH levels. A relative higher occurrence of deranged TSH values in infertile women when compared to control group in this study reflects the tendency of infertile patients towards thyroid insufficiency or vice-versa. A higher occurrence of hyperprolactinemia (59.37%) was seen in infertile women. This higher propensity of hyperprolactinemia is in agreement with the findings of Kumkum et al who had depicted a prevalence of 46% in their study\[15\]. In our study, a significant negative correlation between serum TSH & serum Prolactin levels in infertile women indicates that the rise in serum TSH level is accompanied with a lowering of serum Prolactin levels and vice-versa. Furthermore in our study, the majority of infertile patients and controls were euthyroid. These findings can be explained as follows:

The final common pathway for TSH & prolactin secretion is the thyrotropin releasing hormone (TRH), which stimulates the secretion of both TSH & Prolactin\[16\]. TRH is under negative feedback control of TSH through a short negative feedback loop, any increase in TSH will decrease the release of TRH which in turn will inhibit the secretion of prolactin & will also normalise the TSH levels. A prominent feature of the hormonal cascade is the negative feedback system operating when sufficiently high levels of the ultimate hormone have been secreted into the circulation. Generally, there are three feedback loops- the long feedback, the short feedback, and the ultra-short feedback loops.
The short feedback loop is exemplified by the pituitary hormone that feeds back negatively (TSH in this case) on the hypothalamus operating through a cognate receptor\cite{17} (Figure 2). This explains the normal TSH levels in majority of the cases. Since the study has been conducted in state of Haryana (A region in Sub-Himalayan goitre belt)\cite{18}, the exclusion criteria adopted here is such that majority of women with infertility included in the study are supposedly suffering from hormonal imbalance. Long-standing higher TSH levels due to Iodine deficiency in the study participants has probably resulted in altered prolactin levels. Thus, we can conclude that alteration in TSH levels due to any reason can disturb the Prolactin levels and can cause a failure of conception and maintenance of pregnancy.

PRL secretion is under dual regulation by hypothalamic hormones via the pituitary portal circulation. The predominant regulatory signal is inhibition of PRL secretion by the neurotransmitter dopamine from neurons in the hypothalamus. The stimulatory signal for Prolactin secretion can be mediated by other factors including TRH, TRH also called as, thyrotrophin releasing factor (TRF), Thyroliberin or protirelin is a tropic tripeptide hormone that stimulates the release of TSH and prolactin by the anterior pituitary. The final common pathways of the central stimulatory and inhibitory control of Prolactin secretion are the neuroendocrine organs producing Prolactin Inhibiting Factors (PIF), such as dopamine, somatostatin and gamma-amino butyric acid or prolactin releasing factors (PRF), such as TRH, Oxytocin and neurotensin. PIF and PRF from the neuroendocrine neurons can be released either at the median eminence into the long portal veins or at the neurointermediate lobe which is connected to the anterior pituitary lobe of the pituitary gland by the short portal vessels\cite{16}.

The subjects selected in this study included 50 infertile women in whom the male factor of infertility, tubal factor, any congenital anomaly of the urogenital tract & any obvious organic lesion were ruled out. Thus, subjects with unexplained infertility were included in our study. The TSH & prolactin levels in these study subjects had a significant negative correlation. The altered prolactin levels may contribute to failure of conception & pregnancy as Prolactin is supposed to be important for maintenance of secretory activity of the corpus luteum\cite{19}. Prolactin is a pleiotropic hormone best known for the multiple effects it exerts on the mammary gland. However, it also exerts effects on other targets important to the reproduction of the mammalian species. In some mammals, particularly rodents, prolactin is also important for maintenance and secretory activity of the corpus luteum. In most rodents, Prolactin acts as a leutotropic hormone by maintaining the structural and functional integrity of the corpus luteum for six days after mating. This leutotropic action is characterized by enhanced progesterone secretion. Progesterone is essential for the implantation of the fertilized ovum (along with estrogens), maintenance of pregnancy and inhibition of ovulation\cite{20}. In the absence of Prolactin, the dominant steroid produced by the corpus luteum (of the rat) is 20α-hydroxyprogesterone whose synthesis from progesterone is catalyzed by 20α-hydroxysteroid dehydrogenase\cite{21}.

This metabolite of progesterone is “inactive” in most progesterone bioassays. Prolactin enhances progesterone secretion in two ways: Prolactin potentiates the steroidogenic effect of luteinizing hormone (LH) in granulosa-luteal cell and inhibits the 20α-hydroxysteroid dehydrogenase enzyme which inactivates progesterone\cite{22}.

There are few limitations of our study. The sample size of the study is small but in lieu of the exclusion criteria set by the investigators which excluded all other reproductive causes of infertility, in a way that the subjects included in the study were the true representatives of the women suffering from infertility due to hormonal imbalances. Such a study group will give more reliable results on the infertility due to hormonal causes. The present study is a hospital based study, so the data should be extrapolated to the general population with care to avoid the slightest traces of selection bias. Due to lack of time & resources & for reducing difficulties in recruiting counter parting controls, this study was planned to be conducted in a hospital setting.

**Conclusion:**

There was higher prevalence of hyperprolactinemia with normal thyroid function in infertile patients as compared to fertile ones in the control group. Since a significant correlation exists between serum TSH and prolactin levels, all infertile women both with normal or abnormal thyroid function (be it subclinical or overt, hypothyroidism or...
hyperthyroidism) should also be evaluated for serum prolactin levels.

Acknowledgements:
We are highly grateful to our laboratory technician, Mr. Basant.

References:
4. Indian Council for Medical Research (ICMR) and National Academy of Medical Sciences (NAMS), National Guidelines for Accreditation, Supervision and Regulation of ART clinics in India. New Delhi:Ministry of Health and Family Welfare, Government of India; 2005.