

Association of Thyroid Disorders with the Hormones of Anterior Pituitary in Female Infertility

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ABSTRACT

Background: Fertility in females is centred on the functional hypothalamo-pituitary-ovarian (HPO) axis. Thyroid dysfunctions are also known to interfere with the physiology of reproduction and pregnancy. This study was conducted with an objective to evaluate the relationship between thyroid and pituitary hormones in female infertility because abnormalities of HPO axis and thyroid dysfunction are one of the common and often treatable causes of infertility in females.

Methods: Hundred female patients of infertility who visited the Department of Biochemistry, SGT Medical College, Hospital and Research Institute, Gurgaon for hormonal evaluation were recruited for the study. After excluding other causes of infertility including tubal factors, genetic or other anatomical factors; blood samples for TSH, LH, FSH and Prolactin were collected. Hundred age matched healthy fertile females were recruited as controls and their blood samples were collected for similar hormone assay. These parameters were estimated by the ELISA technique. Results were statistically analysed.

Result: Out of the patients in our study group, 78% had primary infertility while secondary infertility was seen in 22% of the patients. Majority of the patients came out to be euthyroid (79%). There was a significant (p value < 0.05) high serum level of Prolactin in patients of infertility as compared to controls. LH and FSH were found to be lower in infertile patients as compared to healthy controls. Moreover there was a significant positive correlation between the levels of TSH and Prolactin in infertile patients thus it might be imperative to say that hypothyroidism was strongly associated with hyperprolactinemia.

Conclusion: For the normal physiology of reproduction, the functions of pituitary as well as thyroid should be normal. From our study we have elucidated that abnormalities of the thyroid gland and pituitary gland are interrelated. Thus their evaluation becomes necessary in order to elucidate the etiopathogenesis of female infertility which will further enhance the dimension towards designing effective treatment protocols.

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Introduction

Infertility is the inability of a couple to achieve pregnancy over an average period of one year despite of having regular unprotected sexual intercourse.^[1] Infertility can be primary or secondary. In primary infertility, the couples have never been able to conceive; while in secondary infertility the couple has conceived previously but have a difficulty currently with conception.^[2]

There are no reliable estimates for global prevalence of infertility.^[3] The incidence of female infertility is rising and varies from 10 to 20%.^[4] Infertilities, either primary or secondary occurs for almost 15% of all women worldwide.^[5]

Infertility may be caused by an underlying medical condition that may damage the fallopian tubes, interferes with ovulation or causes hormonal complications. To find out the etiology and to treat it successfully; has always been the matter of concern for clinicians and is a potential area of research by researchers. The physiology of reproduction in females depends upon a complex interplay of the Hypothalamo-Pituitary-Ovarian (HPO) axis.^[6] The hypothalamus through the release of gonadotropin releasing hormones (GnRH), controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body. Thus, alterations in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence is a cause of hormonal abnormalities. Hormonal imbalance is an important cause of anovulation. Women with hormonal imbalance will not produce enough follicles to ensure the development of ovum.^[2]

Clinical and experimental studies have suggested a close relationship between Hypothalamo-Pituitary-Ovarian (HPO) axis and Hypothalamo-Pituitary-Thyroid (HPT) axis. The specific thyroid hormone receptors at the ovarian level may regulate the reproductive function. Moreover the influence of estrogens at higher levels of the HPT axis seem to integrate the reciprocal relationship between these two major endocrine axis.^[7]

Hormones from pituitary gland like TSH, prolactin or growth hormone may act synergistically with FSH and LH to enhance the entry of non-growing follicles into growth phase. In addition to this, thyroid hormones may be necessary for maximum production of both estradiol and progesterone.^[8]

It is well known that the function of the thyroid hormones includes modulation of carbohydrates, proteins and fat metabolism, gene expression and also sexual and reproductive function and when the thyroid hormone gets out of balance, many body functions are affected.^[9] Thyroid

dysfunction in females have been found to be associated with anovulatory cycles, decreased fecundity and increased morbidity during pregnancy.^[7,10] Hyperprolactinemia also adversely affects the fertility potential by impairing the pulsatile secretion of GnRH and hence interfering with ovulation.^[11] Moreover it is associated with menstrual as well as ovulatory dysfunctions like amenorrhoea, oligomenorrhoea, anovulation, inadequate corpus luteal phase and galactorrhoea.^[12]

Thus we conducted our study with an objective to elucidate a relationship between thyroid disorders and pituitary hormones i.e. LH, FSH and prolactin in female infertility, thereby further consolidating our knowledge about the complex interplay of the Hypothalamo-Pituitary-Ovarian axis and Hypothalamo-Pituitary-Thyroid axis in female reproduction.

Materials and Methods

Our study was the hospital based case control study where hundred female patients who were suffering from infertility formed our study group. They were the patients who visited the Department of Biochemistry, SGT Medical College, Hospital and Research Institute, Gurgaon for hormonal evaluation. Careful history was taken and the patients of both primary as well as secondary infertility were recruited in the study group. They were subjected to the exclusion criteria where causes of infertility like tubal blockage, cervical factors, pelvic inflammatory diseases or any other infective etiologies, other genetic factors including congenital anomalies of urogenital tract and male factor infertility were taken into consideration.

Hundred healthy fertile females of the similar age groups were taken as controls. After taking the informed consent from both the groups; blood samples for thyroid profile (T3, T4 and TSH), LH, FSH and Prolactin were taken in plain vacutainers on second day of menstrual cycle following standard laboratory procedures. These parameters were assayed by competitive enzyme immunoassay; ELISA using ELISA kit method (Accubind ELISA Microwells). Results were analysed statistically.

Continuous variables were expressed as mean and standard deviation and discrete variables were expressed as a percentage; Student t-test was applied to the values of TSH, T4, T3, LH, FSH and prolactin for the comparison of data in the two groups. Differences were considered as significant if p value was <0.05. Pearson's correlation coefficient was calculated to find out the correlation between different parameters in our study.

Results

Out of the hundred patients of our study group; majority were suffering from primary infertility (78%) and only

22% had secondary infertility. Their age wise distribution is given in **Table 1**.

Mean age of the female patients having primary infertility was significantly lower (23.6±4.78) as compared to the mean age of the female patients with secondary infertility (29.9±5.65)(p value<0.05).

On evaluation of the clinical history, menstrual irregularities were much more frequently present in infertile patients as compared to controls. **Figure 1** shows the distribution of the menstrual cycle patterns in the infertile patients as well as the control group.

It was found that oligomenorrhoea was predominant in infertile females of our study group (48%) followed by amenorrhoea (19%). However menstrual disturbances were also seen in healthy controls in the form of oligomenorrhoea, amenorrhoea or menorrhagia but only in 12% of them and majority had normal menstrual cycles.

Measurement of the hormones has always been considered an important component of the infertility work-up in females; thus estimation of T3, T4, TSH, LH, FSH and Prolactin was done in both the groups (cases as well as controls) in our study.

On comparing the levels of pituitary and thyroid hormones in the cases and control groups; the levels of Prolactin and TSH were significantly higher in patients of infertility as compared to controls (**Table 2**). LH and FSH were found

to be significantly lower in infertile females as compared to the healthy controls.

So, it is evident that there is derangement of the normal hormonal milieu in infertile females. We further divided the patients of our study group (cases) into three sub-groups based upon their TSH values as: euthyroid, hypothyroid and hyperthyroid and compared the levels of different hormones in these sub-groups in order to elucidate the impact of thyroid dysfunction on the pituitary hormone status (**Table 3**).

Out of all the parameters studied, hyperprolactinemia was a consistent finding in all the thyroid disorders. Also LH and FSH levels were lower in infertile females; much more significantly in hypothyroidism than any other thyroid illness.

There was a highly significant positive correlation between prolactin and TSH levels in the infertile patients group (r=0.658; p value<0.001) as depicted in **Figure 2**.

However a negative correlation was found between TSH and LH as well as TSH and FSH but was not significant.

Overall hyperprolactinemia was seen in 56% of the patients of our study group and as far as thyroid dysfunctions was concerned; majority of the patients presented were euthyroid (**Figure 3**)

Further, there was no significant difference between the distribution of the hormonal abnormalities between the patients of primary and secondary infertility in our study.

Table 1: Age-wise distribution of the study group patients and controls.

Age groups (years)	Primary infertility (n=78)	Secondary infertility (n=22)	Controls
20-25	40	04	52
26-30	28	06	36
31-35	10	08	08
>36	0	04	04

Table 2: Comparison of the study parameters between the infertile females and healthy controls.

Study parameters	Normal serum levels	Cases (infertile females) (n=100)	Controls (n=100)	p value
TSH (mIU/ml)	0.39 – 6.16	6.98±3.81	1.23±2.64	<0.05
T3 (ng/ml)	0.49 – 2.02	1.9±0.96	1.6±0.05	NS*
T4 (µg/ml)	4.4 – 11.6	6.6±2.51	7.8±2.96	NS*
LH (mIU/ml)	1.5 – 8.0	2.4±1.19	7.1±3.76	<0.01
FSH (mIU/ml)	2.0 – 10.0	3.1±2.37	8.6±3.01	<0.01
Prolactin (ng/ml)	2.0 – 20.0	34.8±8.43	11.4±5.11	<0.001

(NS* = non-significant p value)

Table 3: Comparison of the study parameters in different disorders of thyroid in the infertile group with the healthy controls

Study parameters	Controls (n=100)	Infertile females (n=100) (Cases)		
		Euthyroid (n=79)	Hypothyroid (n=14)	Hyperthyroid (n=7)
TSH (mIU/ml)	1.23±2.64	4.96±3.04 [*]	11.48±7.03 ^{***}	0.12±0.02 [*]
T3 (ng/ml)	1.6±0.05	1.8±1.26	0.3±0.61 [*]	4.6±1.01 ^{**}
T4 (µg/ml)	7.8±2.96	6.4±1.48	3.8±3.11 ^{**}	18.8±2.96 ^{***}
LH (mIU/ml)	7.1±3.76	5.6±3.11	2.6±3.76 ^{**}	3.1±1.72 ^{**}
FSH (mIU/ml)	8.6±3.01	5.8±2.42 [*]	3.1±2.86 ^{**}	3.4±1.16 ^{**}
Prolactin (ng/ml)	11.4±5.11	26.5±4.76 ^{***}	40.4±4.71 ^{***}	29.4±3.82 ^{***}

p values on comparing with healthy controls:

^{*}*p* value <0.05

^{**}*p* value <0.01

^{***}*p* value <0.001

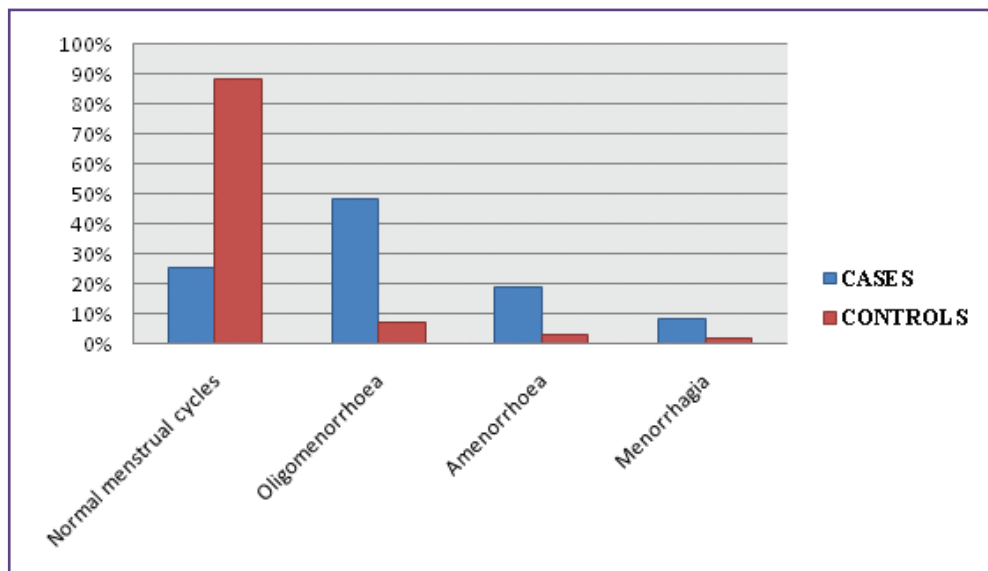


Fig. 1: Distribution of the menstrual irregularities in the infertile patient group and controls.

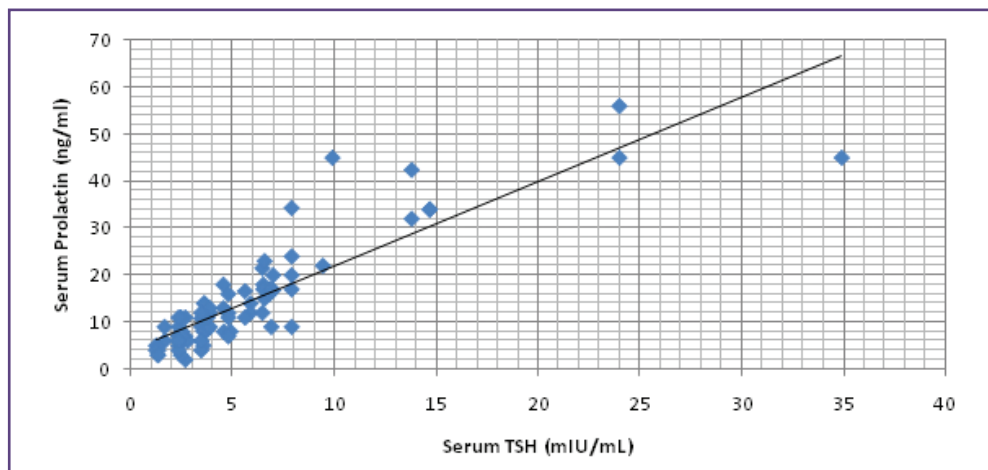


Fig. 2: Correlation between serum prolactin and TSH levels in infertile females.

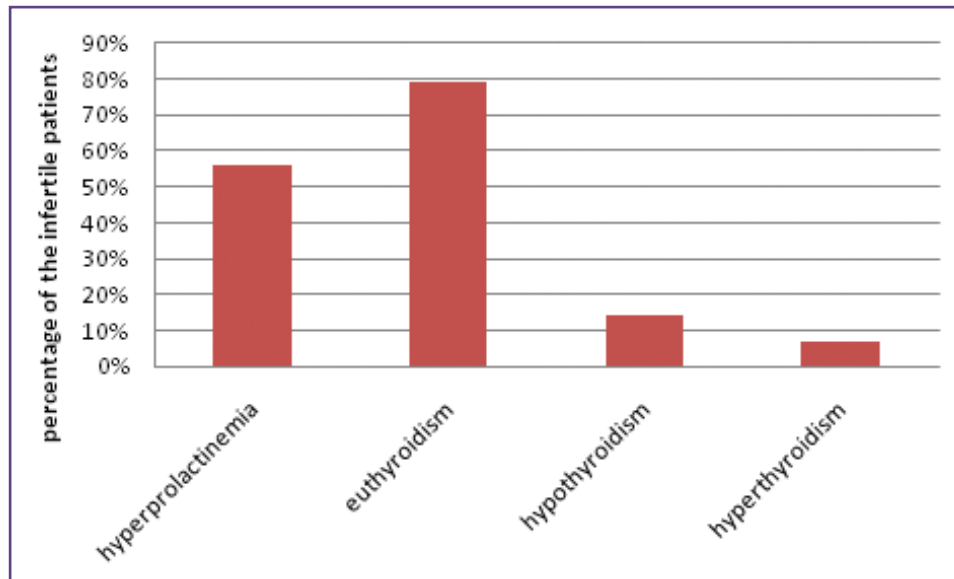


Fig. 3: Distribution of different hormonal profiles in the infertile patients.

Discussion

Infertility, recently has picked up a rising trend and has got not only medical but also psychological as well as economic implications in the human society.^[13]

Hormonal evaluation has been an important aspect of the infertility diagnostic work-up and is also an area of research which forms a basis for the designing of the effective treatment protocols. In our study we evaluated the serum levels of thyroid and pituitary hormones in infertile female patients in order to find out a possible relationship between thyroid disorders and LH, FSH and prolactin. Majority of our patients came out to be euthyroid and hyperprolactinemia emerged as the most frequent hormonal abnormality in the infertile patients of our study.

Prolactin is secreted from anterior pituitary and is primarily associated with breast development during pregnancy and induces lactation. However, prolactin also binds to specific receptors in the gonads, lymphoid cells and liver. Hyperprolactinemia may occur primarily as a result of normal physiological changes during pregnancy, breastfeeding, mental stress, hypothyroidism or sleep. Pathologically it may be due to diseases affecting the hypothalamus and pituitary gland or secondary to disease of other organs such as liver, kidneys, ovaries and thyroid.^[14] Hyperprolactinemia causes infertility by increasing the release of dopamine from hypothalamus which inhibits gonadotrophin releasing hormones and thus gonadal steroidogenesis and eventually infertility.

In our study we found a significant positive correlation between the TSH and prolactin levels in the infertile females.

Thus hypothyroidism can be said to be associated with hyperprolactinemia. It is well documented that in primary hypothyroidism, the serum thyroxine levels are low and there is decreased negative feedback on the hypothalamo-pituitary axis. The resulting increased secretion of thyrotropin releasing hormone (TRH) stimulates the thyrotrophs and lactotrophs, thereby increasing the levels of both TSH and prolactin and thus ovulatory dysfunction due to hyperprolactinemia.^[15]

Thyroid hormones have profound effects on reproduction and pregnancy.^[16,17] Although majority of the infertile patients in our study group were euthyroid followed by hypothyroid, but TSH was frequently present in the upper normal limit in majority of the euthyroid patients when compared with the healthy controls. These might have compensated thyroid functions or raised anti-thyropoxidase antibody titres and must be considered for a thorough investigation. Moreover, despite of the normal TSH and thyroxine levels, some patients might exhibited the clinical picture of hypothyroidism. It has also been documented that 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.^[8]

The final common pathway for TSH and prolactin secretion is thyrotropin releasing hormone (TRH), which stimulates the secretion of both TSH and prolactin.^[18] TRH is under negative feedback control of TSH through a short negative feedback loop and any increase in TSH will decrease the release of TRH which in turn will inhibit the secretion of prolactin and will also normalise the TSH levels. The short

feedback loop is exemplified by the pituitary hormone that feeds back negatively on the hypothalamus operating through the cognate receptor.^[19] This explains the normal TSH levels in majority of the cases.

From our study we have elucidated that most frequent hormonal abnormality in female infertility has been hyperprolactinemia, also seen associated with hypothyroidism. There is a complex interplay between HPT and HPO axis in female reproductive physiology and any derangement in it, leads to anovulatory cycles, luteal phase defects, high prolactin levels, estrogen and progesterone hormonal imbalances.^[14]

Prolactin inhibits the hormones necessary for ovulation i.e. FSH and GnRH. Thus, in the setting of hyperprolactinemia; ovulation is inhibited and contributes to infertility. Moreover when GnRH secretions become low, LH and FSH secretions also fall. So, gamete production is not stimulated and gonadal steroidogenesis is hampered.^[20-22]

In our study also we found that the levels of LH and FSH were low in the infertile patients group; FSH more than LH and that too in hypothyroid patients.

Some of the studies earlier also demonstrated that hyperprolactinemia was associated with a marked reduction in both the frequency and the amplitude of the LH pulses, which indirectly suggested that both the brain and the pituitary gland might be targets for prolactin. The increase which was observed in prolactin may be the cause of the low estrogen and progesterone concentrations in the infertile subjects, which showed that higher serum prolactin concentrations resulted in decreased serum LH and FSH levels in infertile women. Further it was found that there was lower concentration of serum LH and FSH and higher concentrations of prolactin in primary infertile women than in the control group.^[23,24]

Researchers have also found that decreased levels of LH in the midcycle clearly indicate the possibility of anovulation, which could result in infertility. Elevated levels of prolactin in such infertile patients show that there is a mechanism which operates at the anterior pituitary level and leads to abnormal distribution of LH and FSH, thus further explains the abnormal or delayed ovum maturation.^[25] These also corroborate with the findings of our study.

The most frequent menstrual abnormality in our study among the infertile females has been oligomenorrhea. The reason for this might be attributed to the derangement in the normal hormonal milieu which has been seen in the form of hyperprolactinemia may be resulting from longstanding primary hypothyroidism leading on to ovulatory dysfunctions ranging from inadequate corpus

luteal progesterone secretion when mildly elevated to oligomenorrhea or amenorrhea when circulating prolactin levels are high.^[26] In addition to this, 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.

Thus thyroid or pituitary dysfunction can affect fertility in various ways resulting in menstrual abnormalities, anovulation, luteal phase defects to post conception sustenance of the pregnancy.

Conclusion

From the present study it is concluded that there occurs a derangement in hypothalamic-pituitary-ovarian and hypothalamic-pituitary-thyroid axis in female infertility especially in primary infertility. Hyperprolactinemia is seen more frequently as compared to other pituitary and thyroid dysfunctions. Moreover, there is a positive correlation between the levels of TSH and prolactin; TSH and LH in female patients of infertility. Thus, it becomes not only inevitable but also fundamental to evaluate the hormonal status of the females with infertility as it not only gives an insight towards the understanding of its etiopathogenesis but also helps in the designing of the effective treatment protocols.

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Competing interests

None Declared

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