

Prolactin, Thyroid Stimulating Hormone and Thyroid Hormones (Ft3, Ft4) Concentrations in Female Patients with Inferility: An Observational Study

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Abstract

Objective: To determine the variations in thyroid hormones, thyroid stimulating hormone and prolactin levels in females of our population.

Materials and methods:

Subject characteristics: Patients aged 13 to 60 years were studied for their hormonal profile. The inclusion criteria had patients with complaints of mild reproductive and thyroid dysfunction. Patients with severe disorders and cancerous conditions were excluded from the study.

Blood sampling: 3 ml blood was drawn and transferred to clean test tubes. Blood was centrifuged at 3000 rpm for 10-15 min. Serum was separated and stored at -20°C.

Hormonal assay: Thyroid stimulating hormone (TSH), Prolactin, FT3 and FT4 were assayed in the serum. Equipment used in laboratory was Eclecsys 2010 (Roche). Principle of the hormonal test was based on ECL (Electrochemiluminescence). Standard kits by Roche were used for chemical analysis.

The results were analyzed by using ANOVA in SPSS (version 10.0 for windows).

Results: A total of 97 patients were tested. The patients were divided into four major groups, showed overall non-significant variation in hormonal level for Prolactin, FT3 and FT4 ($p > 0.05$). About 80% patients were found normal, in TSH estimation. Women from age 16-35 years old were greater in number than any other age group. Means for each hormone were non-significant at $p = 0.05$.

Conclusion: Hyperprolactinemia causes reproductive disorders in women, early diagnosis and treatment of this disease is important. In conclusion estimation of prolactin and TSH levels might be considered essential in assessment of patient with fertility disorders.

Keywords: FT3; FT4; TSH; Prolactin; Endocrine hormone

Introduction

Measurements of TSH and prolactin are generally included in the evaluation of female infertility [1]. The association between hypothalamic-pituitary-thyroid axis and hypothalamic-pituitary-ovarian axis has been experimentally and clinically proven [2]. Normal thyroid functioning is very important for the normal efficiency of reproduction and maintenance of pregnancy. Thyroid dysfunction interferes with the endocrine regulation of reproductive system [3,4]. Persistent hyperprolactinaemia interrupts the pulsatile secretion of gonadotrophin-releasing hormone thus inhibits the release of luteinizing hormone and follicle-stimulating hormone [5] and directly impairs gonadal sex steroid production.

Subclinical hypothyroidism has also been reported in women with premenstrual syndrome [6]. Whereas relationship between subclinical

hypothyroidism and ovarian function has never been proved by controlled studies [7]. The introduction of the TRH test in 1969 allowed the study of the of thyroid regulation at the hypothalamic and pituitary level in humans much easier [8]. Hypothyroidism reveals various non-specific signs such as increased body weight, depression and is the most common endocrinological problem [9]. Menstrual disturbance, anovulatory cycles and decreased fecundity are caused by over (hyperthyroidism) or under (hypothyroidism) secretion of thyroid hormones [10]. It is documented that overt thyroid dysfunction affects weight no association between either serum TSH or free T4 concentration was found [11]. Hypothyroidism can present with nonspecific constitutional and neuropsychiatric complaints or with hypercholesterolemia, hyponatraemia, hyperprolactinaemia, or hyperhomocysteinaemia. Hypothyroidism is a common disorder, arising more often in women than men and its incidence increases with age. PRL is traditionally named after its lactogenic action (mammogenesis and galactopoiesis included). Animal studies have

shown over 300 identifiable bioactivities of PRL including osmoregulation, reproduction, behavior modification and immune modulation [12]. Objective of our study was to evaluate the variation in Prolactin and TSH concentration at a time with FT3 and FT4 levels in serum of female patients visiting NIH.

Materials and methods

This study was carried out in Reproductive Physiology/Health, PHLD NIH (National Institute of Health, Islamabad) during January 2014-January 2016. 97 female patients were included in this study for endocrinological examination.

Subject characteristics

Patients from age 13 to 60 years were studied for their hormonal profiling. These patients had the complaints of reproductive and thyroid dysfunction. Patients with severe disorders and cancerous conditions were excluded from the study.

Blood sampling

3 ml blood was drawn and transferred to clean test tubes. Blood was centrifuged at 3000 rpm for 10-15 min. Serum was separated and stored at -20°C.

Hormonal assay

Thyroid stimulating hormone (TSH), Prolactin, FT3 and FT4 were assayed in the serum. Equipment used in laboratory was Elecsys 2010 (Roche). Principle of the hormonal test was based on ECL (Electrochemiluminescence). Standard kits by Roche were used for chemical analysis.

Patients groups and data analysis

Mean hormonal concentrations were compared in nine age groups including <20 (Group I), 21-30 (Group II), 31-40 (Group III) and 41-50 (Group IV) at p=0.05. Means ± S.E was calculated for each hormone in respective age group. Number of patients having hormonal concentrations below and above normal range was also calculated. Standard ranges for hormones defined as normal were Prolactin (1.9-25.9 ng/ml), Free T3 (1.45-3.48 pg/ml), Free T4 (0.71-1.85 ng/dL) and TSH (0.32-3.80 µU/ml). Below the minimum limit and above the maximum limit, hormonal imbalance can be a cause of a medical disorder. Four groups were analyzed by using ANOVA in SPSS (version 10.0 for windows).

Results

97 patients were divided into four major groups, showed overall non-significant variation in hormonal level for Prolactin, FT3 and FT4 (p>0.05). About 80% patients were found normal, in TSH estimation. Women with age between 21-30 years were greatest in number than any other age group. Means for each hormone were non-significant at p=0.05.

There was approximately equal deviation in each age group. As the patients claimed medical disorder related to reproductive dysfunction or thyroid malfunctioning, so the values above and below the normal range was found in each age group.

In each age group there were patients with above as well as below concentration of hormones than normal except, in FT3 where there was no case showing hypo FT3 value Table 1.

	Age Mean ± S.D (min-max) Years	No. of patients (N)	Prolactin Mean ± S.D (min-max) ng/ml	TSH Mean ± S.D (min-max) µU/ml	FT3 Mean ± S.D (min-max) pg/ml	FT4 Mean ± S.D (min-max) ng/dL
Group I	17.64 ± 0.42 13.00-20.00	28	30.85 ± 6.50a 10.28-196.10	1.86 ± 0.22b 0.05-4.33	3.69 ± 0.23 a 2.18-7.57	1.92 ± 0.68 a 0.90-20.29
Group II	25.12 ± 0.44 21.00-30.00	41	26.60 ± 3.59 a 5.94-138.40	2.62 ± 0.28ab 0.01-8.61	3.34 ± 0.11 a 2.20-5.51	1.50 ± 0.45 a 0.20-19.57
Group III	35.53 ± 0.74 31.00-40.00	17	22.63 ± 3.31 a 0.47-55.89	1.90 ± 0.23b 0.01-4.05	3.18 ± 0.20 a 2.11-5.22	1.08 ± 0.04 a 0.60-1.37
Group IV	46.55 ± 0.65 43.00-49.00	11	26.68 ± 12.11 a 0.47-145.10	3.45 ± 0.68a 0.64-7.13	3.24 ± 0.16 a 2.56-4.40	1.48 ± 0.39 a 0.95-5.32

Table 1: Mean hormonal concentrations in various age groups in 97 female patients.

Whereas there was a significant variation in all groups for TSH level (P= 0.019) at 95% C.I (Table 1).

Comparison with in the age group showed a variation in TSH level and only group II and IV varied significantly in prolactin concentration (Table 2).

Concentration below the minimum value of normal range is expressed as hypo and greater than maximum limit of normal range in taken as hyper. The respective values falling in these three categories are shown in respective age groups (Tables 3 and 4).

	Prolactin	TSH	FT3	FT4
Group I Vs Group II	Non Sig	Sig	Non Sig	Non Sig
Group I Vs Group IV	Non Sig	Non Sig	Non Sig	Non Sig
Group II Vs Group III	Non Sig	Sig	Non Sig	Non Sig
Group II Vs Group IV	Sig	Non Sig	Non Sig	Non Sig
Group III Vs Group IV	Non Sig	Sig	Non Sig	Non Sig

Table 2: Comparison of Group, 1-IV at 0.05 for each hormone (p<0.05=Sig and p>0.05=Non Sig).

		No. of patients (N)	Prolactin Mean \pm S.D ng/ml	Age Mean \pm S.D years	No. of patients (N)	TSH Mean \pm S.D μ U/ml	Age Mean \pm S.D years
Group I	Hypo↓	-	-	-	1	0.05 \pm 0.0	15.00 \pm 0.0
	Normal→	17	17.36 \pm 1.08	18.00 \pm 0.51	25	1.74 \pm 0.19	17.72 \pm 0.46
	Hyper↑	11	51.68 \pm 14.70	17.09 \pm 0.73	2	4.33 \pm 0.00	18.00 \pm 0.00
Group II	Hypo↓	-	-	-	2	28.00 \pm 2.00	0.06 \pm 0.05
	Normal→	27	15.82 \pm 1.04	25.33 \pm 0.51	30	25.10 \pm 0.54	1.95 \pm 0.13
	Hyper↑	14	47.38 \pm 7.83	24.71 \pm 0.86	9	24.56 \pm 0.78	5.40 \pm 0.53
Group III	Hypo↓	1	0.47 \pm 0.0	32.00 \pm 0.0	1	0.01 \pm 0.0	32.00 \pm 0.0
	Normal→	10	16.22 \pm 1.90	35.30 \pm 0.75	15	1.88 \pm 0.17	35.80 \pm 0.80
	Hyper↑	6	37.01 \pm 4.15	36.50 \pm 1.63	1	4.05 \pm 0.0	35.00 \pm 0.0
Group IV	Hypo↓	1	0.47 \pm 0.0	43.00 \pm 0.0	-	-	-
	Normal→	8	15.09 \pm 2.52	47.50 \pm 0.57	7	2.05 \pm 0.39	46.71 \pm 0.89
	Hyper↑	2	86.16 \pm 58.94	44.50 \pm 0.50	4	5.90 \pm 0.77	46.25 \pm 1.03

Table 3: Concentrations of hormones (Prolactin and TSH) below (Hypo), above (Hyper) and within normal range in respective group of subjects.

		No. of patients (N)	FT3 Mean \pm S.D pg/ml	Age Mean \pm S.D years	No. of patients (N)	FT4 Mean \pm S.D ng/dL	Age Mean \pm S.D years
Group I	Hypo↓	-	-	-	-	-	-
	Normal→	14	2.80 \pm 0.08	17.79 \pm 0.59	27	1.24 \pm 0.04	17.56 \pm 0.43
	Hyper↑	14	4.59 \pm 0.30	17.50 \pm 0.63	1	20.29 \pm 0.0	20.00 \pm 0.0
Group II	Hypo↓	-	-	-	1	0.20 \pm 0.0	27.00 \pm 0.0
	Normal→	38	3.20 \pm 0.08	25.13 \pm 0.47	39	1.07 \pm 0.03	25.15 \pm 0.46
	Hyper↑	3	5.14 \pm 0.19	25.00 \pm 1.53	1	19.57 \pm 0.0	22.00 \pm 0.0
Group III	Hypo↓	-	-	-	1	0.60 \pm 0.0	32.00 \pm 0.0
	Normal→	12	2.73 \pm 0.09	36.08 \pm 0.81	16	1.11 \pm 0.03	35.75 \pm 0.75
	Hyper↑	5	4.26 \pm 0.26	34.20 \pm 1.56	-	-	-
Group IV	Hypo↓	-	-	-	-	-	-

	Normal→	9	3.05 ± 0.11	47.11 ± 0.63	10	1.09 ± 0.04	46.70 ± 0.70
	Hyper↑	2	4.07 ± 0.33	44.00 ± 1.00	1	5.32 ± 0.0	45.00 ± 0.0

Table 4: Concentrations of hormones (FT3 and FT4) below (Hypo), above (Hyper) and within normal range in respective group of subjects.

Discussion

In our study there was no deviation in Prolactin, FT3 and FT4 levels in all the age groups. Whereas TSH values differed predominantly in each age group. A comparison of infertile females with normal showed that abnormal ovulatory function is caused by hypothyroidism and increased TSH levels, which play their important role in infertility [13].

It has been reported that out of 367 infertile women, 95% had clinical disorders such as galactorrhea, luteal insufficiency, and menstrual disturbances and transient hyperprolactinemia was observed at night in 80% of normal prolactin responders who had galactorrhea [14]. It was postulated that patients who exhibit clinical abnormalities such as galactorrhea and luteal insufficiency should undergo extensive prolactin testing.

17 patients had subnormal T4 but normal or elevated T3, suggests that normal T3 levels alone may not be sufficient to maintain euthyroidism. In contrast, there were only three clinically hypothyroid patients who had elevated TSH, normal T4, but subnormal T3 levels [15]. It was shown that the increase of TSH values in boys of prepubertal and pubertal age during maximum physical exercise lasting for 1 h was not related to changes in FT3 or FT4 [16]. Prevalence of hypothyroidism in infertile women was found 6.4% [17,18].

Measurements of TSH and prolactin are generally included in the evaluation of female infertility, but their value in women coming for in vitro fertilization (IVF) has to be assessed. TSH was higher in women whose fertility problem was attributed to a male factor, and prolactin was lower if the measurement was taken during menstruation. TSH and prolactin were positively correlated ($p < 0.0001$) [19]. Thyroid hormone inhibits the expression of the hPRL gene in rat pituitary cells [20] and show the existence of an activating protein-1 (AP-1) response element located at positions 61 to 54 of the proximal promoter, conferring AP-1 stimulation to the hPRL promoter.

The major thyroid hormone (TH) secreted by the thyroid gland is thyroxin T4. Triiodothyronine T3 is formed chiefly by deiodination of T4, is the active hormone at the nuclear receptor, and it is generally accepted that deiodination is the major pathway regulating T3 bioavailability in mammalian tissues [21]. Central hypothyroidism due to hypothalamic or pituitary disorders, the amount of serum thyrotropin can be low because of decreased production or inappropriately normal or only modestly elevated as a result of synthesis of a thyrotropin molecule with reduced bioactivity [22,23].

In hyperprolactinaemic women, the incidence of galactorrhea is up to 80%, depending on the diligence with which galactorrhea is sought [24,25]. Hyperprolactinaemia may be found in 30% of women with secondary amenorrhea, and in 75% of women with both amenorrhea and galactorrhea .

While weight gain is noted to be associated with hyperprolactinaemia, normalization of PRL level resulted in weight loss in one study [26]. Another retrospective study found no correlation between the two [27]. Hyperprolactinaemia may be

associated with subtle psychological symptoms such as anxiety, depression and hostility that occasionally persist even after successful treatment of elevated PRL [28,29].

The prevalence of subclinical hypothyroidism has been estimated, in European and U.S. populations of elderly ambulatory participants, to vary 5-fold from 1.4% in rural Sweden to 7.8% in the Framingham Heart Study [30,31]. Subclinical hypothyroidism appears to be more common in females (7–18%) as compared to males (2–15%) [32-34] and the Whickham survey (British survey of adults of all ages) demonstrated an increasing prevalence with age in women, reaching 18% in those aged 74 years and older, compared with a relatively stable 2–5% in males regardless of age [35]. There are fewer studies defining the prevalence of subclinical hyperthyroidism; however, those that are available also show significant variability, estimates in elderly populations ranging from 0.8% to 5.8%, although typically quoted prevalence of 1.5% in women and 1% in men over the age of 60 years [36,37]. Hyperthyroidism is a common disorder affecting approximately 2% of women and 0.2% of men. Prolactin releasing hormone is involved in the maintains corpus luteum in many species.

Conclusion

It is further suggested to find the correlation of these hormones in various endocrinological and infertility disorders that can lead to infertility. It is therefore concluded that hyperprolactinemia with thyroid dysfunction may be a major contributory hormonal factor in infertility among infertile women and as such, estimation of prolactin, T3, T4 and TSH should be included in the workup for infertile women especially those with hyperprolactinaemia.

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