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A Study of serum Thyroid stimulating hormone levels in pateints with menorrhagia

Biochemistry

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ABSTRACT

Aims &Objectives : 1) To study the serum thyroid stimulating hormone (TSH) levels in 100 females regular menstrual cycle control group & 100 females patients with menorrhagia. 2) To compare the serum TSH levels in 100 regular menstrual cycle control group & 100 patients with menorrhagia. ***Materials&Methods*** : The present study is a cross-sectional observational study with comparison group & has been carried out in Dept. of Biochemistry, GMC, Nagpur from Feb. 2015 to Nov. 2016. A total of 100 patients with menorrhagia aged between 20 – 45 years were selected from the Obs. & Gyn. OPD of GMC, Nagpur & 100 normal healthy females of same age group 20 – 45 years were selected as controls after satisfying all inclusion & exclusion criterias, ethical committee approval & willing to give consent. Serum TSH levels was estimated by one step non competitive immunoenzymatic sandwich ELISA assay using ERBA thyrokit TSH kit. The samples were analyzed by Robonik readwell touch Elisa plate analyzer & Robonik Washwell plate ELISA washer. ***Results :*** The results presented in the table indicates that mean TSH levels were significantly raised (>3.45 µIU/ml) in 23 patients as compared to 11 controls. ***Discussion :*** Prevalence of thyroid dysfunction was higher in females patients with menorrhagia as compared to the normal menstrual cycle females control group & we found that the commonest type of uterine bleeding pattern seen in overt & subclinical hypothyroidism cases was menorrhagia.

KEYWORDS:

TSH, ELISA.

INTRODUCTION

The reproductive period is the most important period in the life span of women which extends from menarche to menopause[1]. Abnormal uterine bleeding in excess amount can lead to anemia, affecting her daily routine activities & health & is a common clinical presentation. Thyroid dysfunction is one of the important etiological factor which disturbs normal hypothalamo-pituitary-ovarian (H-P-O) axis of a woman & hence affects normal menstrual cycle, reproduction & fertility[2]. Thus, hypothalamo-pituitary-thyroid (H-P-T) axis interacts with H-P-O axis making a direct connection between thyroid & reproductive system. As H-P-O axis regulates normal menstrual cycle any abnormality in serum thyroxin levels will affect H-P-T axis which in turn disturbs normal H-P-O axis leading to irregular menstrual cycle & abnormal bleeding from the uterus.

Wiksten A M et al[3] established links between menstruation & thyroid diseases. Ely et al[4] states that any irregular bleeding in nonpregnant patients with menorrhagia, TSH should be evaluated. Four types of thyroid dysfunctions[5] are known to affect menstrual cycle, these are i) Overt hypothyroidism (Increased TSH, decreased T_3 & T_4), ii) Subclinical hypothyroidism (Increased TSH with normal T_3 & T_4), iii) Overt hyperthyroidism (Decreased TSH, Increased T_3 & T_4), iv) Subclinical hyperthyroidism (Decreased TSH, normal T_3 & T_4).

There is evidence support association between hypothyroidism & menorrhagia[6,7]. According to some old studies menorrhagia & oligomenorrhea were most common in patients with hypothyroidism[8]. Studies done afterwards found that patients of hypothyroidism presented with menorrhagia, Polymenorrhagia, metropathia & metorrhagia[9].

After going through all studies, it has been found that any type of menstrual abnormality should be considered as a possible presenting symptom of thyroid dysfunction & it may indicate clinical or subclinical abnormality[10,11].

The studies conducted by Wilansky D L et al[12], Blum et al[13], Menon et al[14] & Doifode CD et al[9] gave encouraging results regarding normalization of menstrual cycle after Levo- thyroxin supplementation in overt hypothyroidism[15,16,17]. Hence the present study was conducted.

MATERIALS AND METHODS

The present study was carried out in GMCH, Nagpur during the period of February 2015 to November 2016. All the subjects were examined & investigated according to predesigned proforma. The study protocol was approved by the ethical committee of GMCH, Nagpur. Informed written consent was obtained from all the study subjects enrolled in the study. A total of 200 subjects (100 cases & 100 controls) were studied after satisfying inclusion & exclusion criterias. INCLUSION CRITERIAS :100 cases were female patients of age group (20-45 years) from Obs. & Gyne. OPD of GMCH, Nagpur who were given provisional diagnosis of menorrhagia were selected. 100 healthy & apparently normal females of same age (20-45 years) group & marital status with normal menstrual cycle were selected. EXCLUSION CRITERIAS : 1) All pregnant females & pregnancy related conditions, 2) Polycystic ovarian disease, Diabetes Mellitus, Tuberculosis, fibroid, adenomyosis, polyps, IUCD, bleeding disorders, 3) All diagnosed cases of thyroid dysfunction & those receiving treatment, 4) Subjects who refused to give written informed consent, 5) Females on drugs like anticoagulants, antipsychotics, corticosteroids, Oral Contraceptive pills (OCP), Serotonin selective reuptake inhibitors (SSRIs), tamoxifen, thyroid hormones, ginseng, ginkgo, soy, Hormone replacement therapy (HRT).

Collection of samples[18] : About 5 ml of fasting (8-12 hour fasting) venous blood sample was collected under all aseptic precautions from ante-cubital vein using sterile needles & syringes without the aid of a tourniquet in a glass tube without additives & allowed to clot for 30 minutes & then centrifuged at 4000 rpm for 10 minutes to separate serum. The samples were stored at 2-8 degree Celsius in refrigerator & was analyzed the next day using Robonik readwell touch Elisa plate analyzer & Robonik washwell plate ELISA washer. Hemolysed & lipemic samples were excluded from the study.

Principle of estimation of TSH[19,20,21] : One step noncompetitive immunoenzymatic sandwich ELISA assay by using ERBA thyrokit TSH kit.

Principle : The ERBA thyrokit TSH kit assay is based on the one step immunoenzymatic sandwich principle in conjunction with the Biotin-Streptavidin technology. Two monoclonal anti-TSH of high affinity & specificity are used : one is labeled with Horseradish peroxidase (HRP) & the other with Biotin while the microplate wells are coated with Streptavidin. Standards, samples & controls are dispensed into the wells, followed by the mixture of 2 labelled anti-TSH. During the incubation the 2 monoclonals bind the TSH molecule to two different and specific sites, & contemporaneously, the Streptavidin immobilizes the forming immunological sandwich to the wells through the binding to the Biotin moiety of the biotinilated antibody. After washing to eliminate the not reacted species the mixture of chromogen/ substrate is added. The reaction is then blocked by adding the Stop solution & the colour developed is measured photometrically. The intensity of the colour is directly proportional within the working range of the assay, to the concenteration of the TSH in the sample. The concenteration of the TSH in a patients sample or controls is then determined by interpolation on the calibration curve.

Normal range of TSH in µIU/ml is 0.39-3.45 (Euthyroid) while in hypothyroidism it is >3.4 & in hyperthyroidism is <0.39.

Statistical analysis : Continuous variables (Age, BMI, TSH, T_3 & T_4 levels) were presented as Mean ± SD (mean ± standard deviation). Categorical variables (Type of uterine bleeding, Thyroid status) were expressed in actual number. Age, BMI, TSH, T_3 & T_4 levels were compared between cases & controls by unpaired t-test. Categorical variables were compared by performing chi-square test. One way ANOVA test was applied to compare Mean BMI in euthyroid, overtly hypothyroid, subclinical hypothyroid & hyperthyroid cases. p<0.05 was taken as siginificant (S), p< 0.001 was taken as highly siginificant (HS) & p>0.05 was taken as non-significant (NS). Statistical software STATA version 10.0 was used for statistical analysis.

OBSERVATIONS & RESULTS

Table 1 : Age wise distribution of cases & controls

Age in years	Cases (n = 100)	Controls (n = 100)	p-value
20-30	20	19	0.798 (NS)
31-40	53	60	0.153 (NS)
>40	27	21	0.14 (NS)
Mean age ± SD	34.83 ± 7.09	34.15 ± 5.72	
Median (Range)	36 (20-45)	30(21-45)	
p-value	0.456 (NS)		

NS – nonsignificant

The difference between mean age of cases & controls was found to be statistically non siginificant (p-value 0.4563).

Fig. 1: Age wise distrribution of cases and controls

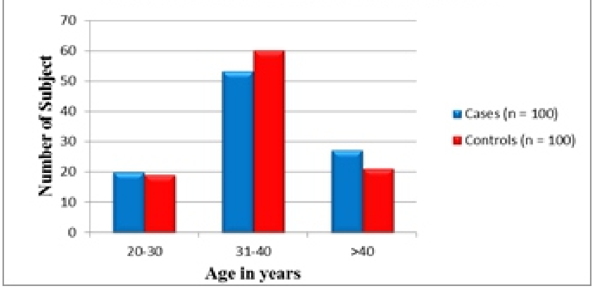


Table 2 : Distribution of cases in relation to uterine bleeding pattern

Uterine bleeding pattern	Number of cases	Percentage
Menorrhagia	51	51
Polymenorrhea	9	9
Oligomenorrhea	19	19
Metorrhagia	2	2
Hypomenorrhea	5	5
Acyclic bleeding	14	14
Total	100	100

The commonest uterine bleeding pattern in all cases was menorrhagia (51%)

Fig. 2. Distribution of cases in ralation to uterine bleeding pattern

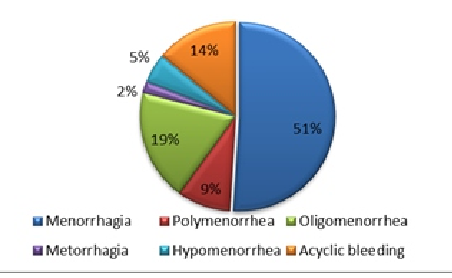


Table 3 : Comparison of BMI status in cases & controls

BMI (Kg/m2)	Cases	Controls	p-value
<18.5 (underweight)	-	3	0.786 NS
18.5-24.99 (Normal weight)	74	85	0.002, S
25-29.99(overweight)	23	11	<0.001 HS
≥ 30 (Obese)	3	1	0.04, S
Total	100	100	

S- significant, HS- highly significant, NS – nonsignificant

Fig. 3. Comparision of BMI status between cases and controls

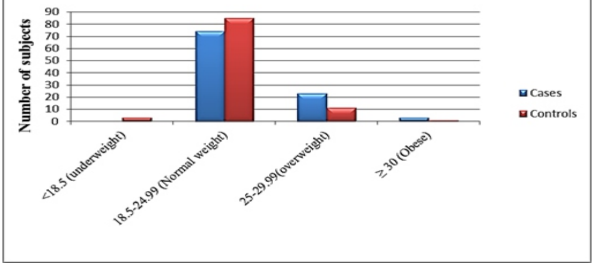
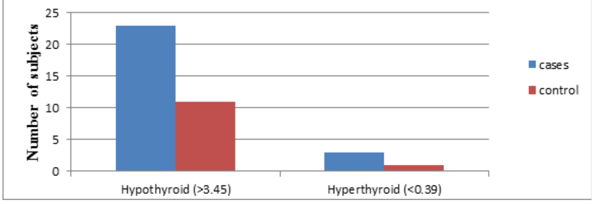


Table 4 : Serum TSH levels in cases & controls

TSH levels (µIU/ ml)	Cases (n=100)			Controls (n=100)			p-value
	Overt	Subclinical	Total	Overt	Subclinical	Total	
Normal Euthyroid (0.39-3.45)			74			88	<0.001, HS
Hypothyroid (>3.45)	9	14	23	3	8	11	<0.001 HS
Hyperthyroid (<0.39)	3	0	3	1	0	1	0.04, S

Mean TSH levels were highly significantly raised (>3.45 µIU/ ml) in 23 cases as compared to 11 controls.

Fig. 4. Abnormal serum TSH levels in cases and controls



DISCUSSION

Normal ovulation requires communication between the hypothalamus, pituitary & ovary. H-P-T axis and the H-P-O axis are physiologically related and act together as a unified system in a number of pathological conditions including infertility, menstrual disturbances and recurrent miscarriages. The suggestion that specific thyroid hormone receptors at the ovarian level might regulate reproductive function, as well as the suggested influence of estrogens at the higher levels of HPT axis, seems to integrate the reciprocal relationship of these two major endocrine axes[22]. Both hypo and hyperthyroidism interfere with HPO axis by altering steroid hormone metabolism, by acting on thyroid hormone receptors (present on oocyte, pituitary, endometrium) and TSH receptors (present on endometrium), alteration in gonadotrophin levels[23,24,25]. Cross-talk between estrogen & thyroid receptors provides multiple and flexible opportunities for relations between two major hormonal systems important for neuroendocrine feedbacks & reproductive behaviours[26].

Hypothyroidism is commonly associated with ovulatory dysfunction due to numerous interactions of thyroid hormones with the female reproductive system. Both hyperprolactinemia due to increased TSH production, & altered GnRH pulsatile secretion, leads to a delay in LH response & inadequate corpus luteum formation leading to anovulation[27,28,29]. This anovulation leads to no progesterone secretion. Unopposed estrogen allows the endometrium to proliferate & thicken. The end result is asynchronous breakdown of endometrial lining at different level of maturation leading to different types of bleeding (i.e; menorrhagia, oligomenorrhea & polymenorrhea).

In the present study, mean TSH value in cases & controls were 6.88 µIU/ml & 2.49 µIU /ml respectively and this difference was found to be statistically highly siginificant. Mean T_4 (7.37 µg/dl vs 8.76 µg/dl) values were compared between cases & controls. Mean T_3 (1.03 ng/ml vs 1.12 ng/ml) levels were also compared but the difference was not siginificant. Based on serum values of TSH, T_4 & T_3, cases were classified into euthyroid, overtly hypothyroid, subclinically hypothyroid & hyperthyroid.

In our study 74% cases were having TSH levels within normal range (0.39 – 3.54µIU / ml), 23% were having raised TSH levels above normal reference range & 3% were having TSH values below normal reference range. The difference were statistically siginificant.

Sharma Neeluet al[30] found increased TSH levels in 22% of DUB cases, while 14% were having decreased TSH levels. Percentage of TSH levels more than normal is same as seen in our study.

TSH forms important part of H-P-T axis. Any increase or decrease in TSH levels in the blood will disturb the balance between HPO & HPT axis, affecting normal ovarian & uterine cycle & will lead to abnormal uterine bleeding from uterus.

Thyroid dysfunction & uterine bleeding patterns : Thyroid dysfunction was commonest in menorrhagia (35.29%), followed by polymenorrhea (33.33%), hypomenorrhea (20%), acyclic bleeding (14.3%) & oligomenorrhea (10.5%). Our findings are in accordance with Moghal (1997)[31]&Padmaleela K et al[32].

In case of hypothyroidism plasma binding activity of Steroid hormone binding globulin (SHBG) is decreased resulting in decreased plasma concenteration of estradiol. Also there are decreased rates of clearance of androstenedione & estrone & further there is increase in peripheral aromatization[33,34,35]. So, these increased levels of estrogen along with anovulation leads to proliferation of endometrium. Asynchronised bleeding of endometrial lining at different levels of maturation leads to change in cycle length & duration & different types of bleeding i.e; menorrhagia, (regular, prolonged duration & increased amount of bleeding), polymenorrhea (increased frequency of bleeding) & acyclic bleeding (no discernable cyclic pattern)[36]. Polymenorrhea, a presumed luteal phase dysfunction, results in shortened cycles (less than 21 days), whereas oligomenorrhea, a prolonged follicular-phase dysfunction, results in lengthened cycles (more than 38 days). Mid-cycle spotting occurs before ovulation as the estrogen levels decline[37]. Menorrhagia is regularly occurring heavy menstrual bleeding (more than 80 ml per cycle) & may result from estrogen breakthrough bleeding. So, in the present study hypothyroidism seen in patients with menorrhagia & polymenorrhea.

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