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Assessment of Thyroid Functions Test among Hyperprolactinemic Sudanese Infertile Females

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Abstract

Background: Hyperprolactinemia is the most prevalent endocrine disorder in hypothalamic- pituitary axis especially among reproductive age women. This cross section study was conducted to assess thyroid function among infertile Sudanese female with hyperprolactinemia.

Methods: One hundred infertile Sudanese females with hyperprolactinemia were chosen for this study and 50 infertile Sudanese females with normal prolactin level were used as controls. All individuals were within the same age group (16-42). Prolactin, LH, FSH, TSH, T4 and T3 were measured in both group by Radioimmunoassay.

Results: 17% of hyperprolactinemic patients were found to be with hypothyroid; interestingly no case was reported to have hypothyroidism or other thyroid dysfunction in the control group. The concentrations of serum PRL and TSH was significantly higher than in the control group while the level of LH and FSH were found to be significantly lower than in the control positive association was found between PRL and TSH among hyperprolactinemic patients.

Conclusions: This study was found an association between hyperprolactinemia and hypothyroidism. The relatively high occurrence of hypothyroidism among hyperprolactemic infertile females emphasizes the importance of estimating both serum prolactin and TSH in infertility.

Keywords: Hyperprolactinemia; Hypothyroidism; Thyroid dysfunction; Infertility

Introduction

Presence of abnormally high values of prolactin >25 µg/L (580 mIU/L) for women is termed as hyperprolactinemia which is one of the most common endocrinological disorder of the hypothalamopituitary axis affecting fertility [1,2]. Hyperprolactinemia affects the fertility potential by impairing pulsatile secretion of GnRH and interferes with the action of gonadotropins at the ovarian level so interfering with ovulation [3,4]. Hyperprolactinemia causes galactorrhea along with menstrual and ovulatory disturbances. It is present in two thirds of women with both galactorrhea and amenorrhea. So estimation of serum prolactin levels should be done in unexplained infertility, any menstrual irregularity with or without hirsutism, galactorrhea with or without amenorrhea, luteal phase defects and anovulation [5]. Mild hyperprolactinemia can cause infertility even with regular menstruation [6]. Women with galactorrhea and hyperprolactinemia might have primary hypothyroidism [5].

Hypothyroidism stimulates increased secretion of TRH which stimulates thyrotrophs and lactotrophs, causing increase in the levels of both TSH and prolactin [7,8].

Materials and Methods

This was a cross-sectional, case control study carried in Khartoum state, Sudan. The study subjects consist of 150 patients. Samples were collected from Nile Fertility Center. 100 samples were collected from hyperprolactinemic patients their age range from 16 to 42 years to be used for the study group. 50 normal prolactin patients with the same age group (16-42) were used as controls. The control group included infertile patients with normal prolactin concentrations.

Sample collection

Venous blood (5 ml) was aseptically collected from the infertile and fertile women by venepunture and dispensed into clean plain bottles, allowed to clot, retracted and centrifuged at 5000 revolution per minute (rpm) for 5 min. The serum obtained was separated and frozen till used for prolactin and thyroid function assay (TSH, T3 and T4 assay).

Assays

All measurements were done using Radioimmunoassay technique, Radioimmunoassay kits for thyroid and thyroid stimulating hormones (TSH, T4, and T3 kits) were obtained from the Department of Isotopes from China Institute for

Atomic Energy (CIAE). Reagents for measuring PRL, LH, and FSH (LH, FSH, and PRL kits) were obtained from Institute of Isotope Ltd. 1535 Budapest, Hungary.

Inclusion criteria

Each woman enrolled in this study must be married, infertile, in reproductive age (16-45), and with hyperprolactinemia to serve as study group.

Exclusion criteria

Patient with tubal factors or any congenital abnormality of the urogenital tract, with a history of thyroid disease or a previous thyroid surgery, or those who were currently on thyroid medication were excluded from this study.

Statistical Analysis

SPSS (version 11.0 (SPSS, Chicago, IL).) was used for the statistical analysis. Prevalence was carried out using Microsoft Excel program. One sample Kolmogorov–Smirnov test was used to check the distribution of variables. The groups were tested for differences by Student's t-test. The relationship between variables was analyzed by Bivairate Pearson`s correlation. Differences and correlations were considered significant at $p<0.05$. The data were initially presented as the mean ± SD.

Results

The prevalence of thyroid dysfunction and its association with hyperprolactinemia was found in 17 women with hypothyroidism (17%), all of them in the study group and there is no any subject had a thyroid dysfunction in control group. The association between hyperprolactinemia and hypothyroidism in **Table 1**.

Thyroid and thyroid stimulating hormones

The mean value of total T4 is (95.7 ± 37.3) for hyperprolactinemic group was slightly lower than the mean value of the total T4 (105.6 ± 16.8) for the control group as shown in **(Table 1)**. The mean value of total T3 was found to be (1.34 ± 0.58) for the hyperprolactinemic group was slightly lower than that (1.45 ± 0.44) of the control group as shown in **Table 1**. These differences were statistically insignificant as shown in **Table 1**. Interestingly, the mean value of thyroid stimulating hormone (11.6 ± 2.64) for hyperprolactinemic group was significantly higher than that of the control group (1.7 ± 1.01) (p=0.008) **(Table 1 and Figure 1)**.

Follicle stimulating (FSH) and lutenizing hormone (LH) and prolactin (PRL)

The mean value of follicle stimulating hormone (9.7 ± 16.53) for hyperprolactinemic group was lower than the mean value for the control group (18.8 ± 21.22), significant difference was found (p=0.003) **(Table 1 and Figure 2)**.

Table 1 Mean ± SD of FSH, LH, T4, T3, TSH, BMI and age among case and control groups.

	Case	Control	P value
Prolactin	2190.34 ± 1471.36 (709.00-5000.00)	243.44 ± 106.19 (70.00-464.00)	0.000
FSH	9.68 ± 16.54 (.30-120.00)	18.83 ± 21.22 (.60-72.10)	0.003
LH	9.20 ± 10.69 (.30-70.00)	14.62 ± 14.61 (.80-70.00)	0.011
T4	95.70 ± 37.28 (5.00-221.00)	105.16 ± 16.77 (68.00-144.00)	0.09
T3	1.34 ± .58 (.10-5.40)	1.44 ± .44 (.80-2.70)	0.255
TSH	11.62 ± 26.41 (.30-90.00)	1.68 ± 1.01 (.40-4.00)	0.008
BMI	25.47 ± 4.43 (19.80-37.20)	23.38 ± 3.059 (20.70-32.20)	0.899
Age	27.05 ± 6.31 (16.00-42.00)	27.22 ± 6.91 (16.00-42.00)	

t-test was used to calculate P value

P value less than 0.05 considered significant

Mean ± Std. Deviation

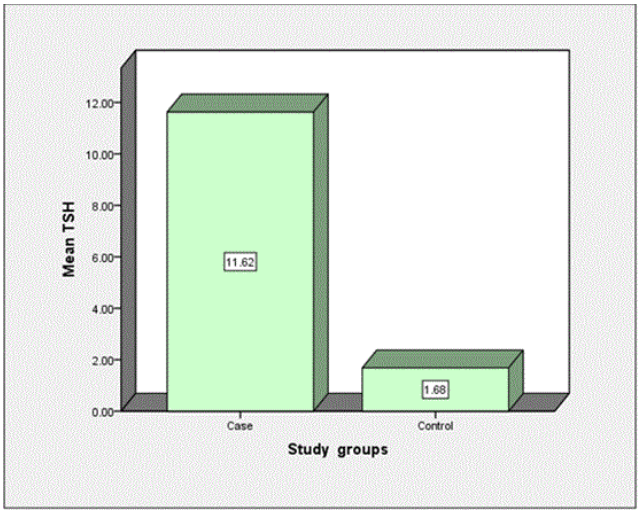

Figure 1 Comparison of mean values of TSH in case and control groups.

The mean value of luteinizing hormone (9.2 ± 10.7) for the hyperprolactinemic group was lower than the control group (14.6 ± 14.7), significant difference was found (p=0.011). The mean value of prolactin level (2190 ± 1471) in the hyperprolactinemic group was clearly very high than the mean of the control group (243 ± 106.2); this confirmed the selection criteria. This difference is statistically significant (p=0.000) **(Table 1)**.

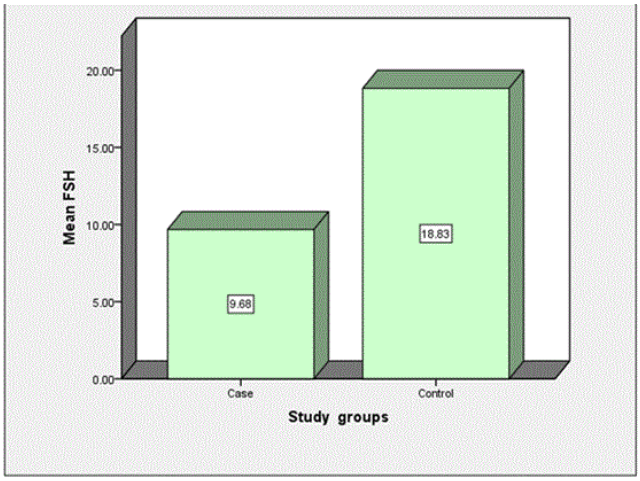

Figure 2 Comparison of mean values of FSH in case and control groups.

Relationship between PRL and TSH

The association between hyperprolactinemia and thyroid disorders, 100 hyperprolactinemic patients were examined for thyroid function test, serum total T4 and T3 and TSH concentrations (TFT) reproductive hormones (FSH, LH, PRL) were also determined. Correlation tests were done to found that TSH was positively significantly correlated with prolactin (p=0.016) **(Figure 3)**. The prevalence of hypothyroidism in hyperprolactinemic patients was determined and it is found to be 17% in the study group. On the other hand correlation between prolactin and (T4 and T3) was statistically insignificant (p=0.763) and (p=0.461) respectively **(Table 2)**.

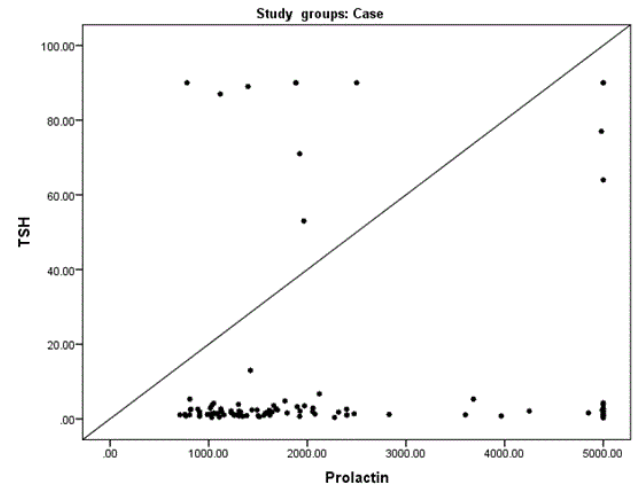

Figure 3 Correlation plot of prolactin hormone against TSH in case group. P value 0.016*.

Correlation between PRL, FSH and LH

FSH was significantly inversely correlated with prolactin (p=0.014). Correlation is significant at the 0.05 level. Correlation between prolactin and LH was statistically insignificant (p=0.297).

Table 2 Correlation of prolactin with FSH, LH, T4, T3, TSH, BMI and age among study group.

Study groups			Prolactin
Case	FSH	R value	0.149
		P value	0.014**
	LH	R value	0.105
		P value	0.297
	T4	R value	-0.031
		P value	0.763
	T3	R value	0.075
		P value	0.461
	TSH	R value	0.24
		P value	0.016*
	BMI	R value	0.896**
		P value	0
	Age	R value	-0.350**
		P value	0
Bivairate Pearson`s correlation was used to calculate the correlation R value=value of correlation			

Correlation of PRL with age and BMI

Prolactin was significantly inversely correlated with age in the study and control group respectively (r=-0.35. p=0.000) (r=-0.397. p=0.004) **(Table 2)**.

And significantly positively correlated with body mass index (BMI) in both group (study r=0.896, p=0.000; control r=0.922. p=0.000) **(Table 2 and Figure 4)**.

Correlation of LH and FSH with age and BMI

FSH is positively correlated insignificantly with BMI in the study group (r=0.194. p=0.054), and insignificantly inversely in control group (r=-0.218. p=0.129). The LH is positively correlated insignificantly with BMI in the study group (r=0.153, p=0.13) and insignificantly inversely in control group (r=-0.106, p=0.464) **(Table 2)**.

FSH was insignificantly inversely correlated with age in the study group (r=-0.100, p=0.32). And significantly inversely in control group (r=-0.294, p=0.038). LH was positively insignificantly correlated with age in the study group (r=0.003 p=0.976) and insignificantly inversely in control (r=-0.203, p=0.157) **(Table 2)**.

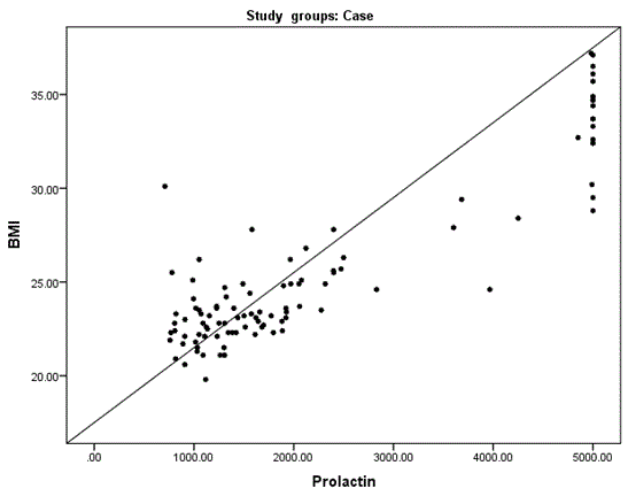

Figure 4 Correlation plot of prolactin hormone against BMI in case group.

Discussion

Despite of the high prevalence of thyroid diseases in the general population, its impact on reproductive function has been the subject of only few well-controlled clinical studies [9]. It is well known that in both sexes thyroid hormones influence sexual development and reproductive function. Hypothyroidism from infancy, if untreated, leads to sexual immaturity and hypothyroidism beginning before puberty causes a delay in onset of puberty followed by anovulatory cycles [10]. It is stated in different textbooks that in adult women, hypothyroidism results in changes in cycle length and amount of bleeding [11,12]. Clinical survey in Sudan suggests that 25% to 50% of women experiencing secondary amenorrhea have elevated prolactin levels. It thus represents a common condition, with important medical, economic and psychological implications. Sub fertility affects one or the two couples are associated with considerable patient stress and anxiety. 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%). Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome. Data on the relationship between thyroid disorders and infertility remain scarce and the association with a particular cause of infertility has not been thoroughly analyzed [13,14].

The increase in prolactin secretion during pregnancy and lactation or pathological due to hypothalamic and pituitary diseases, or it can be iatrogenic. Hyperprolactinemia induces suppression of the hypothalamic-pituitary-gonad axis and resistance of the ovary to gonadotropin action, which results in amenorrhea and lack of ovulation. Hyperprolactinemia cause of infertility in Sudanese patients was extensively studied; one of these important studies was performed at SAEC to determine the reference values of FSH, LH and PRL, progesterone (PG), testosterone and estradiol (E2) in this study high incidences of hyperprolactinemia in Sudanese infertile women and a relatively high incidence among Sudanese males were reported in **Tables 1 and 2**. The study concluded that Hyperprolactinemia is the main cause of amenorrhea among 33% of Sudanese amenorrheic women [15]. More recent study was addressing the concentration of prolactin in pre- and post-ovulatory phases [16]. Nationally, no study was performed to study the effect of thyroid disorder on the infertility, but there was one study investigated and determined the symptoms accompanied with hypothyroidism, one of these symptoms is hyperprolactinemia which is found in 43% of the patients included in the study. This hyperprolactinemia disappeared after treatment with thyroxine [17]. The current study was designed to assess the thyroid dysfunction on hyperprolactinemia. The prevalence of thyroid dysfunction in hyperprolactinemic patients was determined and it is found to be hypothyroidism in 17% of the study group. In this study it was found that 17% of patients in the target group had hypothyroidism but no incidence was reported among subjects in the control group **(Figures 2,3,5)**.

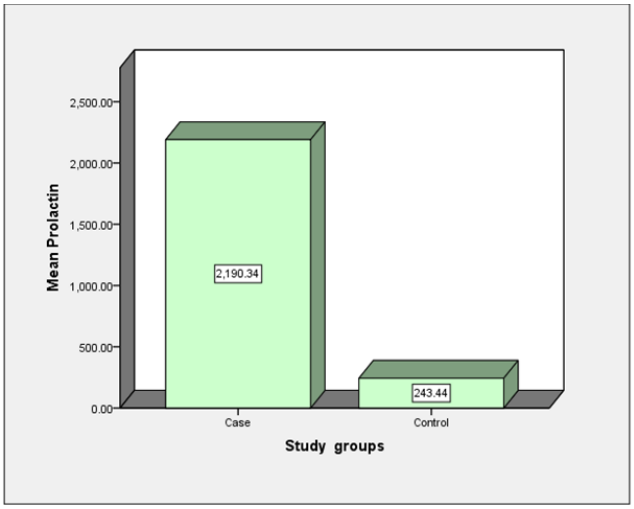

Figure 5 Comparison of mean values of prolactin in case and control groups.

This finding is in complete agreement with many previous studies [18-20]. In these studies hyperprolactinemia due to hypothyroidism varies between 10 and 25%. Some other studies reported smaller percentages compared to our finding in this study, previous study carried out in Finland reported only 4% of the study population had clear hyperprolactinemia associated with hypothyroidism. In the same study the highest percentage of women with an increased serum TSH (>5.5 mIU/L) was observed in the group with ovulatory dysfunction (6.3%), compared to 4.8% in the idiopathic group, 2.6% in the tubal infertility group and non in the endometriosis group [21] **(Figure 1)**. Two other prospective studies observed 0.23% [22] and 2.3% [23] prevalence of hypothyroidism in infertile women without including a control group of healthy fertile women. The relatively high prevalence of hypothyroidism in other

studies may be due to specific referral pattern of the patients who were referred on the basis of suspicion of thyroid abnormalities [24,25]. A relatively high occurrence of increased TSH in otherwise euthyroidism infertile women, as compared to control women, is a common observation in above mentioned studies. According to study done in Pakistan, majority of infertile as well as fertile women of Lahore, were euthyroidism and the apparent difference in frequency of thyroid dysfunctions among them was not statistically significant [21]. Hypothyroidism as a secondary cause of hyperprolactinemia was extensively studied; the treatment of hypothyroidism (administration of thyroxine) is much easier than hyperprolactinemia treatment.

In this study we found that approximately (31%) hyperprolactinemic patients had some kind of menstrual disturbance, while only (8.2%) of the normal controls had irregular periods. Although this finding indicates that the frequency of menstrual disturbances in hyperprolactinemic patient, is approximately three times greater than in the normal prolactin and normal thyroid this is still much lower than the findings of previous similar studies [26]. Similar study results demonstrate that hypothyroidism in women is less frequently associated with menstrual abnormalities than was previously believed. Thyroid antibodies did not correlate with the occurrence of menstrual disturbances in hypothyroidism [27]. The negative correlation of FSH in this study may be due to the selection criteria of the control group that not considering other factors of infertility **(Table 2 and Figure 2)**. According to several case- control studies, normalization of serum PRL levels has been observed after LT4 replacement of patients with overt thyroid failure [28,29]. Importantly, in sub-clinical hypothyroidism elevated basal and stimulated PRL levels have been associated with disturbances in female reproductive function. Thereafter, relevant effects of T4 treatment can be postulated [30,31]. A previous study was conducted to investigate the effect of thyroid hormone replacement on serum PRL regulation in patients with sub-clinical hypothyroidism. A significant reduction in basal PRL levels in L –T4 treated patients was found, confirming earlier reports [32].

In recent *in-vitro* fertilization study, it was observed that women with elevated TSH levels produced oocytes that failed to be fertilized [33]. However, PRL levels in hypothyroid males have been shown to be normal in magnitude suggesting that hypothyroidism is not sufficient to cause hyperprolactinemia [34].

Although the mechanism by which hypothyroidism causes hyperprolactinemia is not completely understood, it is well known that TRH is a physiologic mediator of both PRL and TSH release and thus, elevated hypothalamic TRH levels increase PRL secretion in hypothyroid patients [11,12,35]. Estrogens are known to increase the PRL response to TRH in hypothyroidism [36,37]. Such thyroid under function can affect female reproductive physiology indirectly in a number of ways: altering the pituitary ovarian axis, decreasing the binding activity of sex hormone binding globulin (SHBG) resulting in increased free serum testosterone and Estradiol, decreasing the metabolic clearance of androstenedione and estrone and increasing TRH levels resulting in increased prolactin levels and a delayed LH response to LH-releasing hormone [38]. The higher conception rate after thyroxine supplementation in infertile women with increased TSH verifies the presence of tissue hypothyroidism in such women [39,40]. Instead of simple TSH testing, the use of TRH testing is advocated in many studies for the detection and treatment of hypothyroidism in infertile women [11]. In a comparison of infertile women with different females, the reasons of infertility has revealed that ovulatory dysfunction is particularly associated with hypothyroidism and increased TSH levels [22,24,41]. From this study we see that, not only stimulation of TRH stimulates both TSH and PRL but also inhibition of TRH inhibits both hormones **(Figure 3)**.

Infertility associated with hyperprolactinemia is reversible with treatment, irrespective of the type of treatment. Lowering of prolactin levels to normal or near normal is often necessary to allow ovulation [42]. Traditionally, measurements of prolactin and thyroid stimulating hormones (TSH) have been considered to be very important components of the evaluation of women presenting with infertility [33].

Extremes of weight can influence fertility by affecting ovulatory function [43]. Studies from western countries suggest that intricate and complex hormonal balance of the hypothalamo–pituitary–gonadal axis is affected by an individual's BMI [44]. Obesity has been shown to produce menstrual disturbances and subfertility. Overweight and obese women have been shown to have poorer outcomes following fertility treatment [45]. The severity of obesity and the distribution of fat tissue are important factors that influence the female reproductive system. Obesity has been reported as an increasing problem among women of child-bearing age leading to three times greater risk of infertility in developed countries [46]. This study was found significant association between the level of prolactin and the BMI **(Figure 4)**, and relatively high incidence of overweight among hyperprolactinemic patients, this finding is in complete agreement with recent study in India [18]. The study agree with Kamal Abdelsalam and Waleed Ibrahim who described an association between prolactin and obesity in Sudan [47].

Results of this study noted a significantly inversely correlation between PRL and the age in whole study population, this finding agree with many studies which found an association between PRL secretion and the age [48,49].

Overt hyperthyroidism is well known to be associated with weight loss and, correspondingly, hypothyroidism with weight gain, [50,51]. The study disagree with the result of study conducted by A Nyrnes, and other, in Norway who found serum TSH within the normal range to be significantly and positively associated with BMI in non-smoking men and women [52].

Aging is associated with changes in pituitary-thyroid axis function as well as an increased prevalence of autoimmune and nodular thyroid disease. Previous studies suggested that, in the absence of thyroid disease, aging was associated with

reduced TSH secretion [53,54]. However, more recent data from the National Health and Nutrition Examinations Survey III (NHANES III) show that, in conditions of iodine sufficiency, serum TSH concentrations increase with age in people with no clinical or biochemical evidence of thyroid disease [46].

Conclusion

The present study concluded that hyperprolactinemia and hypothyroidism are important and widely prevalent causes of infertility. Elevated TSH levels were associated with elevated prolactin levels in infertile women's. There is an association between hyperprolactinemia and the hypothyroidism which should be treated measurement of both S. TSH and S. Prolactin levels should be done in all infertile women will allow early and easy treatment of thyroid dysfunction and hence infertility problems.

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