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 μIU/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 venepuncture 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).

|                | Case       | Control    | P value |
|----------------|------------|------------|---------|
| Prolactin      | 2190.34 ± 1471.36 | 106.19     | 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) | 14.61 ± .61 (.80-70.00) | 0.011   |
| T4             | 95.70 ± 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 ± 19.80-37.20) | 23.38 ± 20.70-32.20) | 3.059 0.899 |
| Age            | 27.05 ± 16.00-42.00) | 27.22 ± 6.91 (16.00-42.00) |          |

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

**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).
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).

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).

Correlation of prolactin 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).

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

| Study groups | FSH   | Prolactin |
|--------------|-------|-----------|
| Case         | R value | 0.149     |
|              | P value | 0.014**   |
|              |         |           |
| Case         | 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         |

Bivariate Pearson’s correlation was used to calculate the correlation
R value=value of correlation
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 hypothyroidism 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).

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 subclinical 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 subclinical 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. 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.

**References**

1. Rosato F, Garofalo P (2002) Hyperprolactinemia: from diagnosis to treatment. Minerva Pediatr 54: 547-552.
2. Kadioglu P, Yalin AS, Tiryakioglu O, Gazioglu N, Sanli O, et al. (2005) Sexual dysfunction in women with hyperprolactinemia: A pilot study report. J urol 174: 1921-1925.
3. Zoliner U, Lanig K, Steck T, Dietl J (2001) Assessment of prolactin and gonadotrophic hormones in regulation of the ovarian function. Bangladesh Med Res Counc Bull 16: 1-16.
4. Khana S, Khan AK, Banik NG, Jabeen A (1990) Relationship of prolactin and gonadotrophic hormones in hyperprolactinemia. J Obstet Gynecol India 56: 68-71.
5. Avasti K, Jasmine K, Shweta G (2006) Hyperprolactinemia and Its correlation with hypothyroidism in infertile women. J Obstet Gynecol India 64: 389-399.
6. Eldin S, Abdelghani A, Elmagadum A (2013) Hyperprolactinemia as a cause of female infertility and its prevalence in central Sudan. Egypt J acad Biol Sci 5: 31-36.
7. Asami A, Toru T, Kamimura K, Kinoshita S, Uchiyama M (2001) Precocious puberty in girl with congenital hypothyroidism. J Obstet Gynecol India 64: 389-399.
8. Unuane D, Tournaye H, Velkeniers B, Poppe K (2011) Endocrine disorders & female infertility. Best Pract Res Clin Endocrinol Metab 25: 861-873.
9. Krassas G, Pantikides N (2004) Male reproductive function in relation with thyroid alterations. J Clin Endocrinol Metab 18: 183-195.
10. Gerhard I, Becker T, Eggert-Kruse W, Klinga K, Runnebaum B (1991) Thyroid and ovarian function in infertile women. J Human Reprod 6: 338-345.
11. Thomas R, Reid RL (1987) Thyroid disease and reproductive dysfunction: A review. J Obstet Gynecol 70: 789-798.
12. Longcope C (1996) The male and female reproductive systems in hypothyroidism. In: Braverman L, Utiger R (eds.) Werner and Ingbar’s the thyroid, a fundamental clinical text (7th edn.) Lippincott–Raven, Philadelphia. pp: 849-852.
13. Poppe K, Glinoer D (2003) Thyroid autoimmunity and hypothyroidism before and during pregnancy. J Human Reprod Update 9: 149-161.
14. Poppe K, Velkenier B (2002) Thyroid and fertility. J Endocrinol 64: 389-399.
15. Siddig M (1992) Hormonal change in infertile Sudanese. M.Sc Thesis, Faculty of medicine, Department of Biochemistry, University of Khartoum, Sudan.
16. Hassan A (2001) Local production of donkey anti-rabbits sera for human prolactin radioimmunoassay. M.Sc Thesis, Department of physiology, University of Khartoum, Sudan.
17. Mekki A (1995) Hyperprolactinemia in hypothyroidism and effect of L-thyroxine therapy.
18. Nallusamy S, Gracelyn LJ (2016) Prevalence of hyperprolactinemia in infertile women and its association with hypothyroidism. Int J Adv Med 3: 33-38.
19. Katevu K, Valimaki M, Ketonen L, Lamberg BA, Pelkonen R (1985) Computed tomography of the pituitary fossa in primary hypothyroidism. Effect of thyroxine treatment. J Clin Endocrinol 22: 617-621.
20. Toft AD, Boyns AR, Cole EN, Groom GV, Hunter WM, et al. (1973) The effects of thyrotrphin-releasing hormone on plasma prolactin and thyrotrophin levels in primary hypothyroidism. J Clin Endocrinol 2: 289-295.
21. Elahi S, Tasneem A, Nazir I, Ahmed S, Nagra S, et al. (2007) Thyroid dysfunction in infertile women. J CPSP 17: 191-194.
22. Shalev E, Eliyahu S, Ziv M, Ben-Ami M (1994) Routine thyroid function tests in infertile women: are they necessary? J Obstet Gynecol 171: 1191-1192.
23. Lincoln SR, Ke RW, Kutteh WH (1999) Screening for hyperprolactinemia in infertile women. J Reprod Med 44: 455-457.
24. Arojoki M, Jokimaa Y, Juuti A, Koskinen P, Irjala K, et al. (2000) Hypothyroidism among infertile women in Finland. J Gynecol Endocrinol 14: 127-131.
25. Bals-Pratsch M, Schober O, Hanker JP, De Geyter C, Schneider HP (1993) Disorders of thyroid function and sterility in the women. Zentralbl Gynakol 115: 18-23.
26. Kumkum A, Jasmine K, Shweta G, Ajeshwar NP (2005) Hyperprolactinemia and its correlation with hypothyroidism in infertile women. J Obstet Gynecol India 56: 68-71.
27. Krassas GE, Kaltas NP, Papadopoulou PH, Paunik J, Duntas LH (1999) Disturbances of menstruation in hypothyroidism. J Clin Endocrinol 50: 655-659.
28. Grubb M, Chs D, M WE (1987) Patients with primary hypothyroidism presenting as prolactinomas. J Med 83: 765-769.
29. Gruff AD, Utiger R, Werner J, Ingbar S (eds.) Werner and Ingbar’s the thyroid, a fundamental clinical text (7th edn.) Lippincott-Raven, Philadelphia. pp: 849-852.
30. Olive K, Hennessy J (1988) Marked hyperprolactinemia in subclinical hypothyroidism. J Arch Intern Med 148: 2278-2279.
31. Olive K, Chaffkin L, Kates R, Allan T, Beller P, et al. (2003) Is it necessary to obtain serum levels of thyroid stimulating hormone and prolactin in asymptomatic women with infertility? J Conn Med 67: 393-395.
32. Cooper D, Halpern R, Wood L, Levin A, Ridgway E (1984) L-thyroxine therapy insubclinical hypothyroidism. A double-blind, placebo-controlled trial. J Intern Med 101: 18-24.

33. Cramer D, Sluss P, Powers R, Shane P, Ginsburgs S, et al. (2003) Serum prolactin and TSH in an in vitro fertilization population: Is there a link between fertilization and thyroid function? J Assist Report Genet 20: 210-215.

34. Iranmanesh A, Lizarrlde G, Veldhuis J (1992) Robustness of the male lactoropic axis to the hyperprolactinemic stimulus of primary thyroidal failure. J Clin Endocrinol Metab 74: 559-564.

35. Tolino A, Nicotra M, Romano A, Langella L (1991) Subclinical hypothyroidism and hyperprolactinemia. J Acta European Fertility 22: 275-277.

36. Carlson H, Jacobs L, Daughaday W (1973) Growth hormone, thyrotropin, and prolactin responses to thyrotropin-releasing hormone following diethylstilbestrol pretreatment. J Clin Endocrinol Metab 83: 488-490.

37. Katzneson L, Riskind P, Saxe V, Klibanski A (1998) Prolactin pulseatile characteristics in postmenopausal women. J Clin Endocr Metab 83: 761-674.

38. Takai T, Yamamoto K, Saito K, Ando K, Saito T, et al. (1987) Galactorrhea in subclinical hypothyroidism. J Endocrinol 34: 539-544.

39. Ryff-de-leche A, Statub JJ, Paul S, Polc B, Girard J (1985) Intranasal TSH for the stimulation of hyperphysical and thyroid reserves. J Schweiz Med Wochen 115: 342-343.

40. Edward CRW, Isabel A, Forsyth GM, Besser (1971) Amenorrhea, galactorrhea and primary hypothyroidism with high circulating levels of prolactin. J British Medical 3: 462-464.

41. Strickland D, Whitted W, Wians F (1990) Screening infertile women for subclinical hypothyroidism. J Obstet Gynecol 163: 262-263.

42. Lonescu O, Vuloic C, Lonescu D, Zbranca E (2002) Hyperprolactinemia and pregnancy. J Rev Med Chir Soc Nat Lasi 106: 60-64.

43. Cetin I, Cozzi V, Antonazzo P (2008) Infertility as a cancer risk factor - A review. Placenta 29: 169-177.

44. Chang RJ (2007) The reproductive phenotype in polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 3: 688-695.

45. Pandey S, Pandey S, Maheshwari A, Bhattacharya S (2010) The impact of female obesity on outcome of fertility treatment. J Hum Reprod Sci 3: 62.

46. Bellver J (2009) Body weight and fertility. Reprod Biol Insights 2: 25-30.

47. Abdelsalam KEA, Waleed I (2015) Relationship between TSH, T4, T3 and prolactin in overweight and lean Sudanese PCOS patients. Int J Biomed Res 6: 108-112.

48. Roelfsema F, Pijl H, Keenan DM, Veldhuis JD (2012) Prolactin secretion in healthy adults is determined by gender, age and body mass index. PLoS One 7: e31305.

49. Muldoon MF, Sved AF, Flory JD, Perel JM, Matthews KA, et al. (1998) Inverse relationship between fenfluramine-induced prolactin release and blood pressure in humans. Hypertension 32: 972-975.

50. Baron DN (1956) Hypothyroidism; Its aetiology and relationship to hypometabolism, hypercholesterolaemia, and increase in body weight. Lancet 271: 277-281.

51. Hoogwerf BJ, Nuttal FQ. (1984) Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. Am J Med 76: 963-970.

52. Nyrnes A, Jorde R, Sundsfjord J (2006) Serum TSH is positively associated with BM. Int J Obes 30: 100-105.

53. Mariotti S, Franceschi C, Cossarizza A, Pinchera A (1995) The aging thyroid. Endocr Rev 16: 686-715.

54. Hollowell J, Staehling N, Flanders D, Hannon H, Gunter W, et al. (2002) Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National health and nutrition examination survey (NHANES III). J Clin Endocrinol Metab 87: 489-499.