

Original Article

Association of Thyroid Profile and Prolactin Level in Patient with Secondary Amenorrhea

Sujata SHRESTHA¹, Sunita NEUPANE¹, Narayan GAUTAM¹,
Raju Kumar DUBEY¹, Amit Chandra JHA¹, Nilesh Raj DOSHI²,
Archana JAYAN¹

Submitted: 30 Jan 2016

Accepted: 17 Jul 2016

Online: 5 Oct 2016

¹ Department of Biochemistry, Universal College of Medical Sciences, Ranigaon, Bhairahawa, Nepal

² Department of Gynecology, Universal College of Medical Sciences, Ranigaon, Bhairahawa, Nepal

To cite this article: Shrestha S, Neupane S, Gautam N, Dubey RK, Jha AC, Doshi NR, et al. Association of thyroid profile and prolactin level in patient with secondary amenorrhea. *Malays J Med Sci.* 2016;**23**(5):51–56. <http://dx.doi.org/10.21315/mjms2016.23.5.7>

To link to this article: <http://dx.doi.org/10.21315/mjms2016.23.5.7>

Abstract

Background: Amenorrhea is the absence of menstrual periods. It has multiple social consequences as it may lead to infertility. This case control study was conducted for determining the association of thyroid hormones with hyperprolactinemia in patient with amenorrhea.

Methods: We investigated 50 women with diagnosed cases of secondary amenorrhoea, who attended UCMS hospital, for hormonal evaluations. Fifty two healthy women were taken as the controls. The thyroid dysfunction and serum prolactin level were reviewed in cases and in the controls.

Results: Mean serum prolactin level was found to be significantly higher in the cases as compared to the controls. Mean serum fT₃ and fT₄ level in the hyperprolactinemic cases (mean = 2.67, SD = 1.04 pg/ml) and (mean = 1.38, SD = 0.51 ng/dl respectively) were slightly lower as compared to normoprolactinemic cases (mean = 3.21, SD = 1.86 pg/ml) and (mean = 1.73, SD = 1.37 ng/dl) respectively. Mean TSH of normoprolactinemic and hyperprolactinemic cases were comparable ($P = 0.049$). There was positive correlation between prolactin, BMI and TSH whereas negative correlation of prolactin was seen with fT₃, fT₄ and age. In hyperprolactinemic cases, prolactin was found to be negatively correlated with TSH ($r = -0.155$, $P = 0.491$) whereas prolactin was positively correlated with TSH ($r = 0.296$, $P = 0.126$) in normoprolactinemic cases.

Conclusions: Thus, hyperprolactinemia with thyroid dysfunction may be contributory hormonal factor in patient with amenorrhoea and as such, estimation of prolactin, fT₃, fT₄ and TSH should be included for diagnostic evaluation of amenorrhea.

Keywords: Amenorrhea, prolactin, Thyroid Stimulating Hormone (TSH)

Introduction

Women having regular cycles but lack menses since three months or more and those having irregular or prolonged cycles but absence of menses since nine months or more are taken as secondary amenorrhoeic (1).

Thyroid dysfunctions affect menstrual cycle. Most of the studies have shown the association of thyroid disorder (hyperthyroidism or hypothyroidism) with menstrual disturbance

and even anovulatory cycles (2, 3). Prolactin secretion is regulated by prolactin inhibitor factor secreted from hypothalamus. In addition, other factors like vasoactive inhibitory peptide (VIP) and Thyroid releasing hormone (TRH) also contribute in release of prolactin (4, 5).

Highly elevated levels of prolactin decrease the levels of estrogen in women (6). Pituitary hormones play a vital role in maintaining normal menstruation. Serum TSH, prolactin or growth hormone act synergistically with FSH and LH

that in turn enhance the production of growing follicles (7). Thus, there are certain changes occurred in the follicles in hypothyroidism and it may be due to higher prolactin production that in turn blocks both secretion and action of gonadotropins (8). It was found that even thyroid disorder alone may cause menstrual dysfunction as thyroid hormones are needed for the maximum production of steroid hormones like estradiol and progesterone (9). Hence, the present study can be the baseline data which can show the impact of hormonal changes in thyroid dysfunction and amenorrhea patient and can serve nationwide prevalence for further studies.

Materials and Methods

Case-control study were carried among 102 subjects (50 diagnosed secondary amenorrhoeic patients as cases and 52 healthy subjects as controls by expert Gynaecologist of UCMS from January 2015 to June 2015 in Department of Biochemistry with collaboration of Department of Gynaecology at Universal College of Medical Sciences (UCMS), Bhairahawa, Nepal. Thyroid disorders was classified as euthyroidism, TSH within the normal range, subclinical hypothyroidism, TSH > 4.7mIU/L but normal thyroid hormones, primary hypothyroidism, TSH > 4.7mIU/L and primary hyperthyroidism, TSH < 0.5mIU/L. Likewise, Prolactin level was graded as follows: Hyperprolactinemia, prolactin level more than 23.2ng/ml and normoprolactinemia 1.0 to 23.2ng/ml. Patients on medication that affects thyroid hormone levels, patient with primary amenorrhoea, anorexia nervosa (athletic amenorrhea), Functional Hypothalamic Amenorrhea (FHA), drug induced were excluded. Similarly, patient using any means of contraceptives were also excluded. The consent was taken from each subject and the ethical approval for the study was provided by institute review board of UCMS, Bhairahawa. Serum Prolactin and TSH along with fT₃ and fT₄ were measured by using Perfermed, Human and Diametra kits of ELISA immunoassays respectively.

Statistical analysis

The data generated from study were analysed using IBM SPSS Windows version 22. The data was expressed as mean and SD values. Independent *t*-test, One way Analysis

of Variance (ANOVA) were used. Association between TSH and PRL was analysed with Pearson's correlation coefficient. A *P* value < 0.05 was considered statistically significant.

Results

Thyroid function along with different socio-demographic variables of cases and controls are depicted in Table 1. Out of 50 amenorrhoeic cases taken, 40 (80%) previously had regular cycles but lack menses since three months or more when sample was taken while 10 (20%) previously had irregular or prolonged cycles and lack menses since nine months or more. No significant differences were seen in the mean age (*P* = 0.665) and BMI (*P* = 0.604) between both groups.

Table 1: General characteristics of cases and controls

Characteristic	n (%)	
	Cases	Controls
Euthyroidism	31 (62)	41 (78.8)
Subclinical hypothyroidism	9 (18)	7 (13.6)
Primary hypothyroidism	4 (8)	2 (3.8)
Primary hyperthyroidism	6 (12)	2 (3.8)
Normoprolactinemia	22 (44)	52 (100)
Hyperprolactinemia	28 (56)	0 (0)
Age (yr) ^a	25.92 (7.97)	25.27 (7.12)
BMI (Kg/m ²) ^a	21.89 (3.56)	21.55 (2.91)

^aMean (SD)

Mean serum TSH levels in the amenorrhoeic cases (mean = 4.42, SD = 4.09 mIU/L) were found to be higher than controls (mean = 3.53, SD = 2.4 mIU/L). Likewise, the cases had higher prolactin levels (mean = 23.28, SD = 18.53 ng/ml) than in the controls (mean = 6.57, SD = 4.68 ng/ml) (Table 2). Higher serum prolactin levels were seen in the euthyroidism and subclinical hypothyroidism cases as compared to their respective control groups. Similarly, mean serum prolactin in cases of primary hypothyroidism and hyperthyroidism was found to be significantly higher. (*P* = 0.036) (Table 3).

When we compared fT₃, fT₄ and TSH levels in amenorrhoeic cases with normal and high

prolactin level, we observed that TSH level was higher in the later group whereas fT₃ and fT₄ levels were higher in the former group (Table 4).

There was positive correlation between prolactin, BMI and TSH whereas negative correlation of prolactin was seen with fT₃, fT₄

and age ($P = 0.009$). In hyperprolactinaemic cases, prolactin was found to be negatively correlated with TSH ($r = -0.155$, $P = 0.491$) while positive correlation was seen with TSH ($r = 0.296$, $P = 0.126$) in normoprolactinaemic cases (Table 5).

Table 2: Thyroid hormones, TSH and Prolactin levels in cases and controls

	Cases ^a	Controls ^a	P-value ^b
fT ₃ (pg/ml)	2.91 (1.46)	2.63 (0.79)	0.245
fT ₄ (ng/dl)	1.54 (0.99)	1.37 (0.35)	0.270
TSH (mIU/L)	4.42 (4.09)	3.40 (2.43)	0.334
Prolactin (ng/ml)	23.28 (18.53)	6.40 (4.60)	0.001

^aMean (SD); ^bIndependent *t*-test

Table 3: Comparison of serum prolactin level incases and controls between different Thyroid disorders

	Prolactin level ^a		P-value ^b
	Cases	Controls	
Subclinicalhypothyroidism	18.53 (11.57)	5.68 (4.52)	0.001
Primaryhypothyroidism	35.31 (10.73)	10.21 (1.58)	0.036
Primaryhyperthyroidism	23.43 (19.90)	2.29 (0.29)	0.036

^aMean (SD). ^bAnalysis of variance (ANOVA)

Table 4: Comparison of thyroid hormones and TSH in cases with high & normal prolactin level

	Prolactin ^a		P-value ^b
	Normal	High	
fT ₃ (pg/ml)	3.21 (1.86)	2.67 (1.04)	0.203
fT ₄ (ng/dl)	1.73(1.37)	1.38(0.51)	0.203
TSH (mIU/L)	2.72 (1.90)	5.40 (5.17)	0.049

^aMean (SD). ^bIndependent *t*-test

Table 5: Correlation of prolactin with different parameters in cases

	<i>r</i> ^c	P-value
Age	-0.36	0.009
BMI	0.087	0.550
fT ₃	-0.90	0.535
fT ₄	-0.112	0.438
TSH	0.144	0.319

^c Pearson's correlation coefficient

Discussion

In this study, serum prolactin in cases (mean = 23.28, SD = 18.53 ng/ml) was found to be significantly higher than in control group (mean = 6.40, SD = 4.60 ng/ml). Hyperprolactinemia was seen in 56% of the amenorrhoeic cases.

Similar finding was also observed in the study of Kumkum et al. (10).

Amenorrhea occurs in thyroid disorder due to hyperprolactinaemia as a result of LH and FSH suppression (11). TRH in addition to increasing TSH causes to raise prolactin level (12). Prolactin hinders FSH and GnRH thus

impairs ovulation. Thus, hyperprolactinaemia results to irregular menstrual cycles and infertility (13). Affia Tasneem stated that there was a higher prevalence of hyperprolactinaemia, together with a greater propensity for thyroid disorders in infertile subjects (14).

Majority of amenorrhoeic cases as well as controls were euthyroid in our study. This is supported by study of Elahi et al. (15). In our study, hyperprolactinemia was seen in 75% cases of primary hypothyroidism whereas it was found to be 50% in primary hyperthyroidism. It might be due to small sample size. A study of Singh et al. (16) reported hyperprolactinemia in 57% of women with hypothyroidism. Subclinical hypothyroidism associated with hyperprolactinaemia was significantly higher in our cases than in controls.

Although some studies reported that hyperprolactinemia is rare disorder in subclinical hypothyroidism (17). Tasneem et al. (14) also observed in their study, that some of the women with high prolactin levels had thyroid disorder. In this study, the serum TSH concentration was increased in cases (mean = 4.42, SD = 4.09 mIU/L) as compared to that in the control group (mean = 3.40, SD = 2.43 mIU/L). This is similar to observations made in a study by Sharma et al. (18) Paul Isong et al. (19) and Turankar et al. (9) Positive correlation was found between serum TSH levels and high prolactin level ($P = 0.049$) unlike fT_3 and fT_4 levels in cases. During the regulation of TSH secretion the negative feedback on the hypo-thalamo pituitary axis results in increased secretion of TRH that stimulates thyrotrophs and lactotrophs thereby increasing the levels of both TSH and prolactin (20). Evidence from experimental and clinical studies have suggested that there is a close relationship of hypothalamic-pituitary-ovarian axis (HPO) with hypothalamic-pituitary-thyroid axis (HPT) (20). This study shown an association between amenorrhea and hyperprolactinemia ($P = 0.0001$).

Maximum percentage of the amenorrhoeic group had normal menses whereas 20% had oligomenorrhea. The mean serum levels of fT_3 and fT_4 of the hyperprolactinemic cases were slightly lower than those of normoprolactinemic one. But that was not statistically significant. Similar findings were reported by Poppe and Velkeniers (21).

A positive correlation was found between serum TSH and prolactin levels in cases. This finding is also consistent with the findings of

other studies (22, 23). As we expected, TRH caused hyperprolactinemia in hypothyroidism, perhaps there is some unknown etiology that causes hyperprolactinemia in these cases. Hence, thyroid profile mainly serum TSH and prolactin estimation are ordered clinical tests that are carried out in diagnosing as well as treating amenorrhoeic cases.

Conclusion

In our study, a higher incidence of hyperprolactinaemia was found in amenorrhoeic women. Likewise, thyroid disorders were found to be common in cases. Serum TSH was found to be altered i.e. significantly higher in hyperprolactinaemic subjects.

Acknowledgements

I would like to appreciate Mr. Suresh Prasad Dangol, Ms. Sarita Pyatha and Ms. Sujana Shrestha for their technical support during this research. Also, want to thank all of my teachers and my family for their constant encouragement and motivation.

Conflict of Interests

None

Authors' Contributions

Conception and design: NG
Analysis and interpretation of the data: RKD, ACJ
Drafting of the article: SS
Critical revision of the article for important intellectual content: NG
Provision of study materials or patients: NRD
Statistical expertise: RKD
Administrative, technical, or logistic support: AJ
Collection and assembly of data: SS, SN

Correspondence

Mr. Narayan Gautam
MSc (Universal College of Medical Sciences, Nepal)
Associate Professor
Department of Biochemistry
Universal College of Medical Sciences
Bhairahawa, Nepal
Tel: +977-9847051157
Fax: +977-71-506021
E-mail: ng_bp22@yahoo.com

References

1. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril*. 2004; **82(suppl. 1)**:S33–S39.
2. Poppe K, Velkeniers B. Thyroid disorders in infertile women. *Ann Endocrinol (Paris)*. 2003; **64(1)**:45–50.
3. Poppe K, Velkeniers B, Glinoe D. Thyroid disease and female reproduction. *Clin Endocrinol (Oxf)*. 2007; **66(3)**:309–321. <http://dx.doi.org/10.1111/j.1365-2265.2007.02752.x>
4. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and . *JAMA*. 2004; **14(291)**:228–238. <http://dx.doi.org/10.1001/jama.291.2.228>
5. Harris AR, Christianson O, Smith MS, Fang SL, Braverman LE, Vagenakis AG. The physiological role of thyrotropin-releasing hormone in the regulation of thyroid- stimulating hormone and prolactin secretion in the rat. *J Clin Invest*. 1978; **61**:441–448. <http://dx.doi.org/10.1007/BF02212931>
6. Corrine KW, Robert LB. Etiology, diagnosis, and treatment of secondary amenorrhea [Internet] [updated 2014 April 25; cited 2015 August 22]. Available from: <http://www.uptodate.com/contents/etiology-diagnosis-and-treatment-of-secondary-amenorrhea>
7. Stoffer SS, McKeel DW, Jr, Randall RV, Laws ER., Jr. Pituitary prolactin cell hyperplasia with autonomous prolactin secretion and primary hypothyroidism. *Fertil Steril*. 1981; **36(5)**:682–685. [http://dx.doi.org/10.1016/S0015-0282\(16\)45872-3](http://dx.doi.org/10.1016/S0015-0282(16)45872-3)
8. Wakim AN, Polizotto SL, Burholt DR. Influence of thyroxine on human granulosa cell steroidogenesis in vitro. *J Assist Reprod Genet*. 1995; **12(4)**:274–277.
9. Turankar S, Sonone K, Turankar A. Hyperprolactinaemia and its comparison with hypothyroidism in primary infertile women. *J Clin Diagn Res*. 2013; **7(5)**:794–796. <http://dx.doi.org/10.7860/jcdr/2013/4878.2941>
10. Kumkum A, Jasmine K, Shweta G, Pal Ajeshwar N. Hyperprolactinemia and its correlation with hypothyroidism in infertile women. *J Obstet Gynecol India*. 2006; **56(1)**:68–71.
11. Choudhary SD, Goswami A. Hyperprolactinemia and reproductive disorders-a profile from north east. *J Assoc Physicians India*. 1995; **43**:617–618.
12. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. 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*. 2002; **87**: 489–499. <http://dx.doi.org/10.1210/jcem.87.2.8182>
13. Koutras DA. Disturbances of menstruation in thyroid disease. *Ann N Y Acad Sci*. 1997; **816**:280–284. <http://dx.doi.org/10.1111/j.1749-6632.1997.tb52152.x>
14. Tasneem A, Fatima I, Ali A, Mehmood N, Amin MK. The incidence of hyperprolactinaemia and associated hypothyroidism: local experience from Lahore. *Pak J Nuclear Med*. 2011; **1**:49–55.
15. Elahi S, Tasneem A, Nazir I, Nagra SA, Hyder SW. Thyroid dysfunction in infertile women. *J Coll Physicians Surg Pak*. 2007; **17(4)**:191–194.
16. Singh L, Agarwai CG, Chowdhary SR, Mehra P, Khare R. Thyroid profile in infertile women. *J Obstet Gynecol India*. 1990; **40**:248–245.
17. Gerhard I, Eggert-Kruse W, Merzoug K, Klinga K, Runnebaum B. Thyrotropin-releasing hormone (TRH) and metoclopramide testing in infertile women. *Gynecol Endocrinol* 1991; **5**:15–32. <http://dx.doi.org/10.3109/09513599109049938>
18. Sharma P, Suvama P, Nitin T. Female infertility and its correlation with serum prolactin and TSH concentration- an unmatched case control study. *J Pharm Biomed Sci*. 2013; **30(30)**:902–907.
19. Isong P, Mikau Gali R, Eyo Archibong E, Eze Bassey I, Ekapeudoh A, Ekwerre Elshen O et al. Thyroid hormones and prolactin levels in infertile women in Southern Nigeria. *J Clinical and Diagnostic research*. 2015; **9(3)**:13–14.

20. Emokpae MA, Osadolor HB, Omole-Ohonsi A. Sub-clinical hypothyroidism in infertile Nigerian women with hyperprolactinaemia. *Nig J Physiol Sci.* 2011; **26**:35–38.
21. Poppe K, Velkeniers B. Thyroid and infertility. *Verh K Acad Geneesk Belg.* 2002; **64(6)**:389–399.
22. Raber W, Gessl A, Nowotny P, Vierhapper H. Hyperprolactinemia in hypothyroidism: Clinical significance and impact of TSH normalization. *Clin Endocrinol.* 2003; **58**:185–191. <http://dx.doi.org/10.1046/j.1365-2265.2003.01694.x>
23. Akhter N, Hassan SA. Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh perspective after universal salt iodination. [Internet] *J Endocrinol.* 2009; **5**. Available from: <http://www.ispub.com/journal/the-internet-journal-of-endocrinology/archive/volume-5-number-1-43.html>.