



Prevalence rate of Sudanese Hyperprolactinemic Infertile Females with High thyroid stimulating hormone / high Luteinizing hormone Attended Reproductive Health Care Center –Khartoum (2005-2010).

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ABSTRACT

This was a retrospective study conducted at Reproductive Health Care Center in Khartoum State during the period from 2005 to 2010 to determine prevalence rate of infertile women with hyperprolactinemia and high thyroid stimulating hormone (hypothyroidism) or high luteinizing hormone. A total of 1685 infertile women with high TSH attended the center 1388 (79.4%) with prolactin level within the normal range and 347 (20.6%) women with hyperprolactinemia and high TSH. It was noted that the prevalence rate gradually increased throughout the screening period particularly in the last three years. The prevalence rate increased from 10.5% in 2007 to 21.2% in 2009, with overall prevalence rate =20.6%. Total number of infertile females with high LH and normal prolactin was found to be 1887 (76.2%) and those with high LH and high prolactin were 449 (23.8%). Prevalence rate of women with hyperprolactinemia associated with high LH ranged between 20.1 % to 24.5% but no clear pattern was observed.

المستخلص :

هدفت هذه الدراسة لتحديد معدل الشيوخ للنساء العقيمات ولديهن ارتفاع في هرمون اللين والهرمون المنشط للغدة الدرقية أو الهرمون الملتنوني . تمت الدراسة في مركز رعاية الصحة الإنجابية في الفترة بين 2005 حتى 2010 . عدد النساء العقيمات المترددات على المركز في فترة الدراسة ولديهن ارتفاع في الهرمون المنشط للغدة الدرقية = 1685 . 79.4% هذه المجموعة لديها هرمون اللين في المعدل الطبيعي . ثم إن 20.6% كان لديهن ارتفاعاً في هرمون اللين بالإضافة الى الارتفاع في الهرمون المنشط للغدة الدرقية . معدل الشيوخ إزداد تدريجياً خاصة في الثلاث سنوات الأخيرة حيث إزداد من 10.5% في العام 2007 الى 21.2% في العام 2009 بمعدل شيوخ عام = 20.6% . من ناحية أخرى فإن عدد النساء العقيمات ولديهن ارتفاع في مستوى الهرمون الملتنوني = 1887 . (76.2%) وهذه المجموعة لديها هرمون اللين في المعدل الطبيعي . كذلك فإن 23.8% كان لديها ارتفاع في هرمون اللين بالإضافة الى الارتفاع في الهرمون الملتنوني . بمعدل شيوخ عام تراوح بين 20.1% و 24.5% بتردد غير واضح .

KEYWORDS: *Thyroid gland, infertility, prolactin , hypothyroidism, luteinizing hormone.*

INTRODUCTION

Thyroid function and prolactin are closely interrelated. Long-standing, untreated hypothyroidism is associated with ovulatory dysfunction⁽¹⁾. Measurement of prolactin and thyroid hormones, especially thyroid stimulating hormone (TSH), has been considered as an important component of infertility work up in women⁽²⁾. Thyroid dysfunctions interfere with numerous aspects of reproduction and pregnancy. Some women with galactorrhea and hyperprolactinemia might have primary hypothyroidism⁽³⁾. This is characterized by low serum level of thyroxin and decreased negative feedback on the hypothalmpituitary axis⁽⁴⁾. The resulting increased secretion of thyrotropin – releasing hormone (TRH) stimulates thyrotrophs and lactotrophs, thereby increasing the levels of both TSH and prolactin⁽⁵⁾. Morphological changes observed in the follicles in hypothyroidism can be a consequence of higher prolactin production that may block secretion and action of gonadotrophins⁽⁶⁾. Even in the absence of hyperprolactinemia, hypothyroidism itself may contribute to infertility since thyroid hormones may be necessary for the maximum production of both estradiol and progesterone⁽⁷⁾. In areas with endemic goiter, the major contributor of thyroid dysfunction is iodine deficiency. Infertility associated with thyroid dysfunction in these areas is common⁽⁸⁾. Prolonged untreated hypothyroidism has been reported to cause hyperprolactinemia and increased levels of gonadotrophins mainly follicle stimulating hormone (FSH)⁽⁹⁾. According to Adele, *et al*⁽¹⁰⁾ different increase level of serum prolactin has been reported in 30% of patients with primary hypothyroidism.

They concluded that prevalence of hyperprolactinemia in subclinical hypothyroidism is notable and this disorder is more common in females than in males. There is a high incidence of hyperprolactinemia with a positive correlation of 1:4 between hyperprolactinemia and hypothyroidism⁽¹¹⁾. One of the hormones which increases in infertility is Luteinizing hormone (LH) which is a glycoprotein gonadotropin composed of alpha and beta subunits. LH binds to receptors in the ovary and testis and regulates gonadal function. LH secretion is controlled by gonadotropin releasing hormone (GnRH). High LH indicates failure of feedback mechanism from the ovary indicating infertility⁽¹²⁾. Number of infertile females at reproductive age (18-39 years) visited Reproductive Health Care Center in 2005 was 2307 and the number increased to 2570 in 2010 .1685 of them with high TSH and 1887 with high LH. Investigation of causes of infertility beside hyperprolactinemia is highly recommended particularly TSH and LH which interfere with gonadal functions.

MATERIAL and METHODS

This is a retrospective study conducted at Reproductive Health Care Center – Khartoum during the period 2005-2010.

Inclusion criteria:

Infertile hyperprolactinemic females with high thyroid stimulating hormone / high lutenizing hormone.

Exclusion criteria :

Infertile hyperprolactinemic females with normal thyroid stimulating hormone / normal lutenizing hormone.

Data collection:

Clinical and demographic data of the participants was obtained from Statistical Department of

Reproductive Health Care Center, Khartoum.

Prevalence rate of infertile women visiting Reproductive Health Care Center during the period from January
 Period prevalence rate =

2005 to December 2010 was calculated according to the Kars *et al* ⁽¹³⁾ using period prevalence rate which is calculated according to the following formula:

Every instance of the investigated disease within a defined time period

Average (At risk) population during the time period

Thyroid stimulating hormone (TSH) was determined by Immunoradiometric assay (IRMA). Luteinizing hormone was determined by Enzymatic immunosorbance assay (EIA).

increased throughout the screening period. 11.3% prevalence rate of study group was recorded in 2005 which increased to 21.2% in 2009, with overall prevalence rate = 20.6%. Frequency of infertile women with hypothyroidism and normal prolactin serum level ranged between 60.1% and 90.4% of study population. Prevalence rate of infertile women with hypothyroidism and hyperprolactinemia gradually increased from 11.3% to 39.9 % in 2005 and 2008 respectively (table 1).

RESULTS

The total number of females with high TSH was 1685. 1338 (76.4%) were with normal prolactin level, while 347 (20.6 %) were with high prolactin level. Prevalence rate of infertile women with hypothyroidism gradually

Table .1 Prevalence rate of Sudanese Infertile Women with Hyperprolactinemia and TSH > 4.5 U/L (2005-2010)

Year	No of women with PRL ≤ 400 IU/L		No of women with PRL > 400 IU/L		Total No of study group		Prevalence Rate / 100
2005	227	88.7%	29	11.3%	256	100%	11.3
2006	206	90.4%	22	9.6%	228	100%	10.5
2007	234	86.7%	27	10.3%	261	100%	10.5
2008	223	60.1%	148	39.9%	371	100%	20.2
2009	232	75.3%	76	24.7%	308	100%	21.2
2010	216	82.2%	45	17.2%	261	100%	20.6
Total	1338	79.4%	347	20.6%	1685	100%	20.6

Prevalence rate of infertile women with high LH ranged between 21.3% and 24.5% (table 2). Frequency of infertile women with high LH and normal prolactin level increased from 78.7% in 2005 to 82.0 % in 2007 then decreased to 79.0 % in 2010.

Prevalence rate of infertile women with hyperprolactinemia and high LH = 21.3 % in 2005 and increased to 34.6% in 2008 with overall prevalence rate = 23.8%.

Table 2. Prevalence rate of Sudanese Infertile Women with Hyperprolactinemia and LH > 9.6 U/L (2005-2010)

Year	No of women with PRL ≤ 400 IU/L		No of women with PRL > 400 IU/L		Total No of study group		Prevalence rate / 100
2005	218	78.7%	59	21.3%	277	100%	21.3
2006	134	75.0 %	45	25 %	179	100%	22.8
2007	445	82.0 %	97	18 %	542	100%	20.1
2008	189	65.4 %	100	34.6	289	100%	23.4
2009	179	70.0 %	77	30 %	256	100%	24.5
2010	273	79.0.%	71	21 %	344	100%	23.8
Total	1438	79.2 %	449	23.8	1887	100%	23.8

DISCUSSION:

Most of the women with hypothyroidism having serum prolactin within the normal range. Prevalence rate of women with both hypothyroidism and hyperprolactinemia increased throughout the screening period. Vidal *et al* ⁽¹⁴⁾ reported that higher prevalence of hypothyroidism and hyperprolactinemia in infertile women compared to fertile women, resulting in menstrual disorders which agreed with Goswami, *et al*, ⁽¹⁵⁾ who stated that hypothyroidism is commonly associated with hyperprolactinemia resulting in ovulatory failure, hence assessment of serum TSH and prolactin level are mandatory in the work of all infertile women specially with those with menstrual irregularities. Several mechanisms have been proposed for the increased serum prolactin level in primary hypothyroidism, of these mechanisms, attributed to increased prolactin secretion under the influence TRH which stimulates TSH as well PRL secretion ⁽¹⁶⁻¹⁸⁾. Thyroid hormones themselves may play an important role in the cause of hyperprolactinemia, Davis *et al* ⁽¹⁹⁾ noticed that 3,5,3-triiodothyronine reduces prolactin messenger RNA levels in rodents

pituitary cells thus decreasing thyroid hormones levels resulting in increased prolactin synthesis. Thyroid releasing hormone (TRH) is considered as a stimulant factor for rising prolactin level, estrogen may cause increase prolactin response to TRH that causes higher prolactin level in women ⁽¹⁰⁾. Pituitary adenoma was observed among one third of patients with incidence of hypothyroidism in women with hyperprolactinemia=25.%, in other studies=16.6% ⁽¹¹⁾. The relatively high occurrence of abnormal TSH levels in women with ovulatory dysfunction and oligomenorrhea emphasizes the importance of TSH screening in these women. Other pathological factors leading to hyperprolactinemia in primary hypothyroidism might involve actions on prolactin receptors as well as on prolactin gene expression ⁽¹⁸⁾. The overall prevalence rate of infertile women with hyperprolactinemia and hypothyroidism in this study = 20.6%. Moreover, hyperprolactinemia is present in 36 to 57 % of hypothyroidism patients. Greenspan and Gardner ⁽¹²⁾ reported that approximately 40% of patients with primary hypothyroidism present with a minimal increase in prolactin level (25-30 ng/ ml) and 10% with even

higher Serum levels compared to (20.6%) in the present study. Since patients with primary hypothyroidism have an increase in thyroid releasing hormone (TRH) which stimulates TSH and prolactin release leading to hyperprolactinemia, the authors concluded that the prevalence of hyperprolactinemia in subclinical hypothyroidism patients is considerable, since hyperprolactinemia causes reproduction disorders in women, early diagnosis and treatment of this disease is important. In Sudan, Shabbo *et al* ⁽²⁰⁾ reported that 13.6% of hyperprolactinemic patients were found to be hypothyroid, which showed clear association between hypothyroidism and hyperprolactinemia. High prevalence rate of infertile women with hyperprolactinemia and LH may be due to pituitary nonfunctioning tumors which synthesized glycoproteins such as LH. Moreover, LH secretion is episodic with secretory bursts mediated by GnRH. The amplitude of these bursts is greater in patients with primary hypogonadism ⁽¹²⁾

CONCLUSION

Prevalence rate of infertile females with hyperprolactinemia associated with high TSH increased throughout the screening period particularly the last three years. Infertile females with hyperprolactinemia and high LH showed higher prevalence compared to infertile hyperprolactinemic females with high TSH. Prevalence rate of hyperprolactinemic infertile females visited the center during screening periods also increased ..

REFERENCES

1. Oliver A, Chaffkin L, Kates R, Allan T, Beller P, and Graham N. (2003) .Is it necessary to obtain serum levels of thyroid stimulating hormone and prolactin in a symptomatic women

with infertility?. *J.Conn Med* . **67**(7):393-395.

2. Cramer DW, Sluss PM, Powers RD, McShane P, Ginspurgs ES, and Hornstein MD. (2003) Serum prolactin and TSH in an vitro fertilization population: is there a link between fertilization and thyroid function ? . *J Assist Reprod Genet* . **20** (6): 210-2115.

3. Dousfas AG, and Mastorakos G. (2000) The hypothalamic- thyroid and the female reproductive system. *Ann NY Acad Sci* . **900**: 65-76.

4. Poppe K, Velkeniers B, and Glinoeer D.(2007).Thyroid disease and female reproduction. *Clin Endocrino (Oxford)*. **66** (3): 390-21, Review.

5. Kumkum K, Jasmine K, Shweta G ,and Pal Ajeshwar. (2006) . Hyperprolactinemia and its correlation with hypothyroidism in infertile women. *J Obstet Gynecol India*. **56**(1): 68-71.

6. Armada- Dias L, Carvalho JJ, Breitenbach MM, Franci CR. And Moura EG. (2001). Is the infertility in hypothyroidism mainly due ovarian or pituitary functional changes ? .*Braz. J Med Bio Res*. **34** (9):1209-15.

7. Wakim AN, Polizotto SL, and Burholt DR. (2009).Influence of thyroxin on human granulose cell steroidogen. *J Reprod Infertil* . **10** (3):274-7.

8. Zimmerman MB, Jooste PL, Pandav CS. (2008) .Iodine deficiency disorders. *Lancet* **372** (9645):1251-62.

9. Asami A, Toru T, Kamimura K, Kinoshita S. and Uchiyama M .(2001). Precocious Puberty in girls with congenital hypothyroidism receiving continuous L- thyroxin-replacement therapy. *Pediatrics International* . **43** :87-90.

10. Adele B, Ozra A, Zahra K. and Zakiie V. (2011) Hyperprolactinemia in association with subclinical hypothyroidism. *Caspian J Intern Med* . **2** (2):229-233.

11. Avasthi Kumhum, Kaur Jasmine, Gupta Shweta and Narang Pal Ajeshwar. (2006). Hypoprolactinemia and its correlation with hypothyroidism in infertile women. *J Obstet Gynecol India*. **56** (1):68-71.
12. Greenspan, Frances S. and Gardner David G., (2004). *Basic Clinical Endocrinology*. 7th edition. McGraw-Hill.
13. Kars M, Souverein PC, Herings RM, Romijn JV, Vandenbroucke JP, de Boer A. and Dekker OM. (2009) Estimated age – sex- specific incidence and prevalence of dopamine agonist treating Hyperprolactinemia. *J Clin Endocrinol Metab*. **94**:2729-2734.
14. Vidal E, Kovacs K, Cohen S, Lioyd R. and Scheithauer B.(2000) Transdifferentiation of somatotrophs to thyrotrophs in the pituitary in patients with protracted primary hypothyroidism. *J. Virchows Arch*. **436**:43-51.
15. Goswami B, Patel S, Chatterjee M, Koner BC, and Saxena A. (2009) . Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. *J Reprod Infertil* .**10**(3):207-12.
16. Ezzat S, Asa SL, Couldwell WT, Bare CE, Vance ML, and Mc Cutcheon. (2004). The prevalence of pituitary adenomas: a systematic review. *Cancer*.**101**:613-619.
17. Serri O, Chilk CL, Ur E, and Ezzat S.(2003).Diagnosis and management of hyperprolactinemia .*CAM J*.**169**:575-81.
18. Kroese JM, Grootendorst AF, and Schelfhout LJ.(2004). Postpartum amenorrhoea- galactorrhoea associated with hyperprolactinemia and pituitary enlargement in primary hypothyroidism. *Net J Med*. **62**(1): 28-30.
19. Davis JR, Lynam TC, Franklyn JA, Docherty K. and Sheppard MC. (1986). Tri-iodothyronine and phenythion reduce prolactin messenger RNA levels in cultured rat pituitary. *J Endocrinol* .**109**: 359-364.
20. Shabbo NM, Eltayeb EA, and Ali AM. (2009). Hypothyroidism as underline cause of hyperprolactinemia in Infertile Sudanese Women (un published data).