ORIGINAL ARTICLE

NORTH BENGAL MEDICAL COLLEGE JOURNAL [2020], VOL., 6, No. 1 : 22-28

Hypothyroidism and Hyperprolactinemia among Sub-fertile Patients attending a clinic in Sirajganj

Mst Shakina Khatun[1] *Mahbuba Begum[2]

ARTICLE INFO

Article history:

Received: 08 July 2019

Accepted: 12 October 2019

Online:

www.nbmc.ac.bd

Keywords:

Hypothyroidism, Sub-fertility

Hyperprolactinemia

ABSTRACT

Introduction: *Thyroid dysfunctions are relatively common among women of reproductive age, and can affect fertility in various ways, resulting in anovulatory cycles, high prolactin levels, and sex hormone imbalances. On the other hand, excessive prolactin secretion causes reproductive dysfunction and sub-fertility by decreasing the pulsatile release of Gonadotrophin releasing hormone. So, measurement of TSH and PRL should be routinely done as a part of sub-fertility workup.* ***Methods:*** *This is cross-sectional analytic study done in a private clinic from September 2016 to August 2019. A total 359 patients from Sirajganj or neighbouring districts, having either primary or secondary sub-fertility, were enrolled in this study. As a part of sub-fertility workup, TSH and Prolactin level in serum of these patients were done by hormone analyzer. The results were analyzed by SPSS version 25.* ***Results:*** *Among 359 sub-fertile patients, maximum (44.0%) came from 15-25 years age groups. Mean age of the respondents was 23.23±4.13 years. Out of them, 74.4% had primary sub-fertility and 25.6% had secondary sub-fertility. Majority (88.9%) of them were euthyroid (TSH 0.40-5mIU/L), rest (11.1%) were hypothyroid. Nobody in this study was hyperthyroid. On the contrary, majority (55.2%) of the patients were hyperprolactinemic, the rest had normal prolactin in their serum (1-20ng/L). Duration of marriage was 5.64±3.61 years in primary and 8.05±4.43 years in secondary sub-fertility. Out of 40 hypothyroid patients, 28(70%) had hyperprolactinemia, whereas, out of 319 euthyroid patients, 170(53.3%) had the same. Interestingly 28(7.8%) patients had both hypothyroidism and hyperprolactinemia. Mean TSH level was 2.75±1.89mIU/L in primary and 2.73±2.10mIU/L in secondary sub-fertility. Mean prolactin level was 29.25±24.19ng/L and 25.41±22.80 ng/L in the respective variety of sub-fertility. A strong correlation between TSH and prolactin in the serum of sub-fertile patients was found in this study.* ***Conclusion:*** *Measurement of TSH and PRL should be done at early stage of infertility check up. This can avoid more costly tests or invasive procedures at the very beginning by giving medical treatment only.*

[1] *Assistant Professor, Department of Obstetrics and Gynecology, Shaheed M Monsur Ali Medical College, Sirajganj, Bangladesh*

[2] *Associate Professor, Department of Obstetrics and Gynecology, Shaheed M Monsur Ali Medical College, Sirajganj, Bangladesh*

***Corresponding author:** ✉ dr.mahbubabegum@yahoo.com*

INTRODUCTION

Human sub-fertility is a complex problem, which has numerous consequences depending on the society and cultural background, gender, lifestyle, sexual history of the people it affects. Sub-fertility is a global public health concern, this is partly due to its complexity in aetiology as well as difficulty in preventing, diagnosing and treating it.[1] According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), sub-fertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[2] The term primary sub-fertility is used for a couple who have never achieved a pregnancy despite cohabitation and regular sexual intercourse and secondary sub-fertility is used for a couple who had previously succeeded in achieving at least one pregnancy, even if it had ended in abortion. Worldwide around 8 to 12% of the couples experience some form of sub-fertility during their reproductive lives.[3] This has led the problem of sub-fertility to be recognized as a public health issue.[4] The cause of sub-fertility lies within the female in 45% of the couples, male factor sub-fertility in 30% and in the remaining 25% the cause is unexplained.[5]

The main causes of female sub-fertility include ovulatory disorders, pelvic inflammatory disease (PID), endometriosis, polycystic ovarian syndrome, and advanced age, environmental and occupational exposure to chemicals, congenital abnormalities and hormonal imbalance.[6] Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and subfertility.[7] Thyroid dysfunction reduces the chances of pregnancy and also adversely affects pregnancy outcome.[8] Prevalence of hypothyroidism in the reproductive age group is 2–4% and has been shown to be the cause of sub-fertility and habitual abortion.[9,10] Thyroid dysfunction can affect fertility in various ways resulting in anovulatory cycles, luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalances. Therefore, normal thyroid function is necessary for fertility, pregnancy, and to sustain a healthy pregnancy, even in the earliest days after conception. Thyroid evaluation should be done in any woman who wants to get pregnant with family history of thyroid problem or irregular menstrual cycle or had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse. Hypothyroidism can be easily detected by assessing TSH levels in the blood. Hyperprolactinemia, the presence of abnormally high levels of prolactin in the blood, is the most common endocrine disorder of the hypothalamic-pituitary axis with the prevalence ranging from 0.4% in an unselected normal adult population to as high as 9-17% in women with reproductive disorders.[11,12]

Excessive prolactin secretion causes reproductive dysfunction and sub-fertility by decreasing the pulsatile release of Gonadotropin releasing hormone (GnRH). It impairs pituitary production of Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) and causes other disorders like amenorrhea and galactorrhoea.[13,14] It has been recommended that in the presence of raised PRL, the treatment should be first given to correct the hypothyroidism before evaluating other causes of raised PRL. Measurement of TSH and PRL is routinely done as a part of sub-fertility workup. As hypothalamic thyrotropin releasing hormone (TRH) increases the secretion of both TSH and prolactin, serum prolactin levels may be increased in cases of hypothyroidism.[15] Hypothyroidism and hyperprolactinemia are found to be closely interrelated.[16] This study intends to assess the status of thyroid and prolactin hormone levels and their relation in patients of sub-fertility.

METHODS

The study enrolled 359 female subjects who were suffering from primary and secondary sub-

fertility. The cases were selected in a private clinic over a period of three years. The inclusion criteria for the selection of cases were diagnosis of sub-fertility, age between 15-35 years and duration of marriage more than one year. The exclusion criteria that were adopted during case selection were male factor sub-fertility and amongst the female factors-tubal factor, any congenital anomaly of the urogenital tract, or any obvious organic lesion. Any history of thyroid disease or previous thyroid surgery or being on thyroid medications was also excluded from the study. The participants were enrolled after signing on informed consent. Two milliliters of fasting venous blood was obtained in the morning of day three of menstrual cycle for serum biochemical analysis. Serum was separated and stored for further analysis. All the hormones were estimated using an analyzer ELISA Microplate Reader Biogen-6500 (Made in Germany) and reagent Nova Tec$^{(R)}$ was used for the purpose. The normal range of serum Prolactin and TSH were 1-20ng/ml and 0.4-5mmol/L, respectively.

The following are the operational definition used in this study.

I. Euthyroidism: TSH is within the normal range.
II. Hypothyroidism if serum TSH is >5mIU/L.
III. Hyperprolactinemia when serum Prolactin >20ngm/ml.

Statistical analysis was done by using SPSS software, version 25. A *p*-value of<0.05 was considered statistically significant. Descriptive analysis, Chi-square test, unpaired student's t test and Pearson's correlation test were done for analysis of the results.

RESULTS

Among the total 359 enrolled women, highest no (158, 44%) of sub-fertility was found in 21-25 years age group. The mean age of the respondents was 23.23±4.13 years. Among them, 267(74.4%) patients were with primary sub-fertility and 92(25.6%) patients with secondary sub-fertility. Out of the sub-fertile patients, majority-(319, 88.9%) were euthyroid and 40(11.1%) were found to be hypothyroid. In contrast, a higher number of patients showed prolactin level more than normal. Out of 359 sub-fertile patients, 161 (44.8%) had normal prolactin and 198(55.2%) had hyperprolactinemia (Table I).

Table I: Distribution of the sub-fertile patients according to characteristic (n-359)

Variables	Frequency	Percentage
Age group (years)		
≤ 20(15-20)	117	32.6
21-25	158	44.0
26-30	67	18.7
31-35	17	4.7
Mean±SD (Range)	23.23±4.13(18-35) years	
Type of Sub-fertility		
Primary infertility	267	74.4
Secondary infertility	92	25.6
THS status		
Hypothyroid (> 5.0 mIU/L)	40	11.1
Euthyroid (0.40- 5.0 mIU/L)	319	88.9
Prolactin status		
Normal (1-20ng/L)	161	44.8
Hyperprolectemia (> 20 ng/L)	198	55.2

Mean duration of marriage in primary and secondary sub-fertility were 5.64±3.61years and 8.05±4.43 years respectively. Duration of marriage was significantly (*p*<0.001) associated with primary and secondary sub-fertility (Table II).

Table II: Duration of marriage and it's association between primary and secondary Sub-fertility (n-359)

Duration of Marriage (In years)	Sub-fertility		*p*-value
	Primary (n-267) No. (%)	Secondary (n-92) No. (%)	
2-4	124(46.4%)	17(18.5%)	
5-7	70(26.2%)	32(34.8%)	
8-10	46(17.2%)	24(26.1%)	
11-13	17(6.4%)	11(12.0%)	
>13	10(3.7%)	8(8.7%)	
Mean±SD	**5.64±3.61**	**8.05±4.43**	**<0.001***

Unpaired student's t test, *Significant

Out of 40 hypothyroid patients 28(70%) had hyperprolactinemia and among 319 euthyroid patients 170(53.3%) had hyperprolactinemia. Hypothyroidism was significantly associated with hyperprolactinemia (Table III).

Table III: Distribution of sub-fertile patients according to hormonal status (n-359)

Prolactin	TSH (mIU/L)		*p*-value
	Hypothyroid(n-40) No.(%)	Euthyroid (n-319) No.(%)	
Normal	12(30.0%)	149(46.7%)	0.045*
Hyperprolectemia	28(70.0%)	170(53.3%)	
Total	**40 (100.0%)**	**319(100.0%)**	

Chi-square test, *Significant

Chi square test showed that hypothyroidism was significantly associated with hyperprolactinemia (*p-0.045*). At same time, 28 patients had both hypothyroidism and hyperprolactinemia, whereas 331 patients had either of the two or none (Table IV).

Table IV: Frequency of both hypothyroid and hyperprolactenaemia of the study patients (n-359)

Both hypothyroid and hyperprolactinemia	Frequency	Percentage
Yes	28	7.8
No	331	92.2
Total	**359**	**100.0**

Of the 267 primary sub-fertile patients, mean TSH level was 2.75±1.89 mmol/L and 92 secondary sub-fertile patients had mean TSH level of 2.73±2.10 mmol/L (Table V).

Table V: TSH and prolactin status in sub-fertile patients

TSH status	Sub-fertility	
	Primary(n-267)	Secondary(n-92)
Hypothyroid(>5.o *mIU/L*	29(10.9%)	11(12.0%)
Euthyroid(0.40-5.*0mIU/L*	238(89.1%)	81(88.0%)
Mean±SD	2.75±1.89	2.73±2.10
Prolactin status		
Hyperprolactinemia>20 ng/L	161(60.3%)	37(40.2%)
Normal(1-20 ng/L)	106(39.7%)	55(59.8%)
Mean±SD	29.25±24.19	25.41±22.80

On the contrary, the primary and secondary sub-fertile patients had mean prolactin level of 29.25±24.19ngm/ml and 25.41±22.80ngm/ml respectively. Pearson's correlation test was done between TSH and prolactin in two varieties of sub-fertility which showed highly significant relation (Table VI).

Table VI: Pearson's correlation of TSH with prolactin in primary and secondary sub-fertility (n-359)

Type of Infertility		TSH	
		r-value	*p*-value
Primary Sub fertility	Prolactin	+2.19	*<0.001*
Secondary Subfertility	Prolactin	+.285**	0.006

Scatter diagram in Figure 1 showed the trend of both hormones of increasing in both types of fertilities.

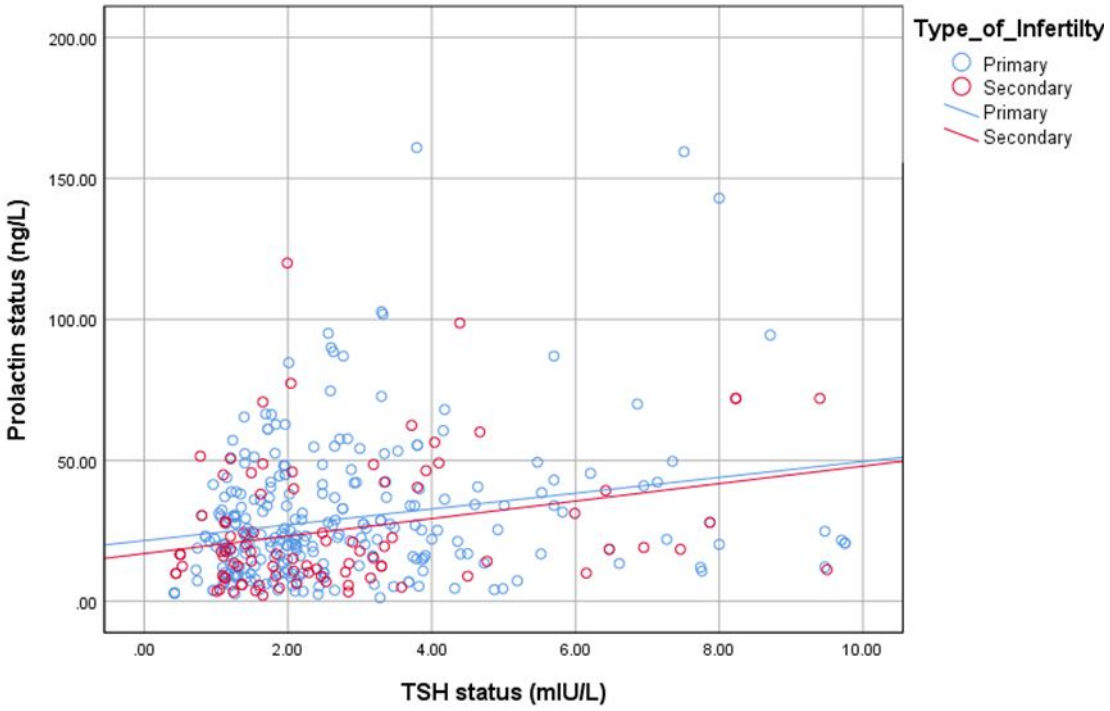

Figure 1: Scatter diagram showing the correlation between TSH and prolactin in primary and secondary sub-fertile patients

DISCUSSION

Thyroid hormones have profound effects on reproduction and pregnancy**.** The prevalence of hypothyroidism in women of reproductive age (20-40 years) varies between 2% to 4%.[17,18] Thyroid dysfunction is a common cause of sub-fertility which can be easily managed by correcting the appropriate levels of thyroid hormones.[19,20] In our study, 40 patients out of 359 had hypothyroidism (11.1%). Relatively higher rate of hypothyroidism was found due to special referral pattern of sub-fertile patients to the clinic. Singh *et al* found 57% of women with hypothyroidism in their study.[21] Elder et al in there cohort study found 20.5% sub-fertile women had associated subclinical hypothy-roidism.[22] In our study, majority of sub-fertile patients had hyperprolactinemia (55.2%). This higher propensity of hyperprolactinemia is in agreement with the findings of Kumkum et al [23] who had depicted a prevalence of 46% in their study. Another study found a higher prevalence

of hyperprolactinemia in primary sub-fertility (60.3%) than in secondary sub-fertility (40.2%).[24] It has been recommended that in the presence of raised TSH along with raised PRL levels, the treatment should be first to correct the hypothyroidism before evaluating further causes of hyperprolactinemia. Hormone therapy with thyroxine is the choice of treatment in established hypothyroidism. It normalizes the menstrual cycle, PRL levels and improves the fertility rate. As per our study, we observed 7.8% sub-fertile patients with hypothyroidism exhibiting hyperprolactinemia. In our study, the mean TSH level in primary and secondary sub-fertility was 2.75±1.89 mIU/L and 2.73±2.10 mIU/L respectively. A study showed that women who never achieved basal TSH <2.5 mIU/L had lower conception rates.[25] Out of 359 patients prolactin level was found to be 29.25±24.19 ngm/L and 24.41±22.80 ngm/L in primary and secondary sub-fertility respectively. Choudhary and Goswami[26] observed hyperprolactinemia in 16.6% patients with hypothyroidism. A significant positive correlation between TSH and Prolactin levels was found in subjects enrolled in our study ($r = 0.219$, $p<0.001$) in primary sub-fertility and $r=0.285$ ($p= 0.006$) in secondary sub-fertility. This finding is also consistent with the findings of Goswami et al.[27] Similar findings were reported by Poppe and Velkeniers.[28] They observed that in hyperprolactinemic patients without any sign of pituitary dysfunction, there are normally reduced levels of thyroid hormones. Tasneem et al.[29] also observed in their study, that some of the women with high prolactin levels had subclinical hypothyroidism.

CONCLUSION

It is therefore, concluded that thyroid dysfunction with hyperprolactinemia may be a major contributor hormonal factor in sub-fertility. Measurement of TSH and PRL should be done at early stage of sub-fertility check up rather than straight away going for more costly tests or invasive procedures.

Conflicts of Interest: There is no conflict of interest.

REFERENCES

1. KL Wright. Defining infertility: what infertility means for clinicians and clients. Network. 2003; 23(2): 4–6.
2. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. The International committee for monitoring assisted reproductive technology (ICMART) and the World health organization (WHO) revised glossary on ART terminology, 2009. Human Reproduction.2009; 24(11): 2683-2687.
3. Cong J, Pingping L, Zheng L, Jichun. Infertility: a tabulation of available data on prevalence of primary and secondary infertility program on Maternal and Child Health and Family Planning, Division of Family Health. World Health Organization, Geneva; 1991. 2016.
4. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Human Reproduction.2007; 22(6): 1506-1512. https://doi.org/10.1093/humrep/dem046.
5. Blundell R. Causes of infertility. International Journal of Molecular Medicine and Advance Sciences. 2007; 3(1): 63-65.
6. Evers MC. The infertile couple. Am Fam Physician. 2002; 54(3): 1001–1010.
7. Thomas R, Reid RL. Thyroid disease and reproductive dysfunction: a review. Obstet and Gynecol. 1987; 70(5): 789-798.
8. Trokoudes, Krinos M, Skordi SN, Picolos, MK. “Infertility and thyroid disorders.” Current Opinion in Obstetrics and Gynecology. 2006; 18(4): 446-451.
9. Lincoln R, Ke RW, Kutteh WH. Screening for hypothyroidism in infertile women. J Reprod Med. 1999; 44: 455–457.
10. Krassas GE. Thyroid disease and female reproduction. Fertil Steril. 2000; 74: 1063–1070.
11. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000; 80(4): 1523-1631.

12. Biller BMK, Luciano A, Crosignani PG, Molitch M, Olive D, Rebar R et al. Guidelines for the diagnosis and treatment of hyperprolactinemia. Journal of Reproductive Medicine for the Obstetrician and Gynecologist.1999; 44(12): 1075-1084.
13. Cooke PS, RHolsberger D, JWitorsch R, WSylvester P, MMeredith J, ATreinen K, et al. https://www.sciencedirect.com/science/article/pii/S0041008X03004721-!Thyroid hormone, glucocorticoids, and prolactin at the nexus of physiology, reproduction and toxicology. Toxicology and Applied Pharmacology. 2004; 194(3): 309-335.
14. Crosignani PG. Management of hyperprolactinemic infertility. Middle East Fertility Society Journal. 2012; 17(2): 63-69.
15. Krassas GE. Thyroid disease and female reproduction. Fertility and Sterility. 2000; 74(6): 1063-1070.
16. Affia T. The incidence of hyperprolactinaemia and associated hypothyroidism: local experience from Lahore Centre for Nuclear Medicine, Mayo Hospital Lahore, 2 Government College for Boys Gulberg Lahore. PJNM. 2011; 1: 49–55.
17. Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. Endocrinol Metab Clin North Am. 1997; 26(1): 189–218.
18. Bjoro T, Holmen J, Krüger O, Midthjell K, Hunstad K, Schreiner T, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol. 2000; 143(5): 639-647.
19. Davis LB, Lathi RB, Dahan MH. The effect of infertility medication on thyroid function in hypothyroid women who conceive.Thyroid. 2007; 17: 773–777.
20. Dajan CM, Saravanan P, Bayly G. Whose normal thyroid function is better –yours or mine? Lancet. 2002; 360: 353–354.
21. Singh L, Agarwai CG, Chowdhary SR, Mehra P, Khare R. Thyroid profile in infertile women. J Obstet Gynecol India. 1990; 40: 248–253.
22. Eldar Geva J, ShohamM, Rosler A. Subclinical hypothyroidism in infertile women: the importance of continuous monitoring and the role of thyrotrophin releasing hormone stimulation test. Gynecol Endocrinol. 2007; 23: 332-337.
23. Kumkum A, Jasmine K, Shweta G, Pal Ajeshwar N. Hyperprolactinema and its coorelation with hypothyroidism in infertile women. J Obstet Gynecol India. 2006; 56(1): 68–71.
24. Akhter N, Hassan S. Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh perspective after universal salt iodination. Internet J Endocrinol. 2008; 5(1): 1-6.
25. Raber W, Nowotny P, Vytiska-Binstorfer E, Vierhapper H. Thyroxine treatment modified in infertile women according to thyroxine-releasing hormone testing: 5 year follow-up of 283 women referred after exclusion of absolute causes of infertility. Hum Reprod. 2003; 18: 707–714.
26. Choudhury SD, Goswami A. Hyperprolactinemia and reproductive disorders--a profile from north east. J Assoc Physicians India. 1995; 3(9): 617–618.
27. Goswami B, Patel S, Chatterjee M, Koner BC, Saxena A. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J Reprod Infertil. 2009; 10(3): 207–212.
28. Poppe K, Velkeniers B. Thyroid and infertility. Verh K Academy Geneeskd Belg. 2002; 64(6): 389–399.
29. Tasneem A, Fatima I, Ali A, Mehmood N, Amin MK. The incidence of hyperprolactinaemia and associated hypothyroidism: local exsaperience from Lahore. Pak J Nuclear Med. 2011; 1: s49–55.