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Serum gonadotropin and prolactin levels in females with primary infertility and thyroid dysfunction in North Indian population

A. Yadav[1*], M. Arora[2], V. Saini[2], J. Bhattacharjee[2], A. Jain[2]

1. Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India
2. Lady Hardinge Medical College, New Delhi, India

Abstract

Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function. Patients with subclinical hypothyroidism have no symptoms or very few symptoms related to thyroid disease, but may have adverse outcome on fertility but are not referred to infertility clinics. Galactorrhea and hyperprolactinemia patients may have primary hypothyroidism. The aim of this study was to evaluate if thyroid dysfunction leads to any alteration in serum gonadotropin and prolactin levels contributing towards infertility. This case control study was performed in 256 females in a tertiary care hospital.Serum TSH, fT4 and fT3, LH, FSH and prolactin levels were assayed using fully automated chemiluminescent immunoassay Analyzer Access 2 by Beckman and Coulter (USA). Serum LH, FSH levels were significantly low and serum prolactin levels were significantly high in patients with infertility and hypothyroidism. Serum LH, FSH levels were significantly high in infertile females with hyperthyroidism whereas serum prolactin levels were low but not significantly different in these patients. Thyroid disorders have a great impact on fertility in females. Fertility improves when euthyroidism is restored. It has been suggested that normal gonadotropin and thyroid function tests are necessary to achieve maximum fertilization rate and blastocyst development. Thyrotoxicosis in women has been linked with reduced fertility but the mechanism for the same has not been elucidated clearly. We suggest screening of thyroid hormone in all the females with infertility.

Keywords: Gonadotropin, Prolactin, Primary infertility, Thyroid dysfunction

1. Introduction

Infertility is defined as failure to conceive after one year of regular intercourse in females < 35 years of age not using contraception and after six months in women > 35 years of age (1). Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function . Approximately 20% of infertile women have thyroid dysfunction and hypothyroidism is a more common disorder in these women as compared to hyperthyroidism (2).

The changes in fertility caused by thyroid dysfunction in women are complex. Cross-talk between the hypothalamic–pituitary–gonadal axis and the hypothalamic–pituitary–thyroid axis has effects on fertility in females (3).

Hypothyroidism leads to fertility problems including impaired ovulation, fertilization, implantation, miscarriage and late pregnancy complications (4). Patients with hyperthyroidism or overt hypothyroidism are likely to be detected before they are referred to infertility treatment clinics, but this is not the case in patients with subclinical hypothyroidism as patients have no symptoms or very few symptoms related to thyroid disease, but may have adverse outcomes on fertility (5).

Hyperprolactinemia leads to infertility by impairing pulsatile secretion of gonadotropin releasing hormone and thus interfering with ovulation (6, 7). In women hyperprolactinemia usually presents with menstrual abnormalities like ame norrhea, oligomenorrhea or galactorrhea and even if women with hyperprolactinemia have regular menses, luteal-phase abnormalities have been suggested to be the

[*]**Corresponding Address:** Dr. Amita Yadav, Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India. Email: dramita.md@gmail.com

cause of infertility (8, 9). Some of the women with galactorrhea and hyperprolactinemia might also have primary hypothyroidism. The aim of this study was to evaluate if thyroid dysfunction leads to any alteration in serum gonadotropin and prolactin levels contributing towards infertility.

2. Materials and methods

This case control study was performed in 256 females in a tertiary care hospital. The inclusion criteria for the selection of cases were diagnosis of primary infertility, age between 20-35 years and not using any contraception for more than one year. Thyroid function test (freeT3, freeT4 and TSH) was performed and females were divided into 3 groups. Group A consisted of 151 females with hypothyroidism and group B consisted of 55 females with hyperthyroidism. Serum LH, FSH and prolactin levels were estimated on 2nd day of menstrual cycle in these patients and their levels were compared with 50 euthyroid females with no reproductive abnormalities (group C).

Cases with male infertility and females with infertility due to anatomical defects in reproductive system (tubal occlusion, cervical adhesions etc) were excluded from the study. After overnight fasting, 5mL venous blood was collected; centrifuged (5 min at 3000 x *g*) and then serum was separated for hormone analysis.

Serum TSH, fT4 and fT3, LH, FSH and prolactin levels were assayed by using system packs of fully automated chemiluminescent immunoassay Analyzer Access 2 by Beckman and Coulter (USA). Reference intervals of TSH is 0.34-5.6µIU/L, fT3 2.5-3.9pg/mL, and serum fT4 0.6-1.12 ng/dL.

Subjects with TSH, fT3 and fT4 levels within the reference range were considered as euthyroid. Patients with TSH levels > 5.6 µIU/mL were taken as hypothyroid. These patients were further divided into subclinical hypothyroidism (TSH- 5.7 to 9.9 µIU/ml with normal fT4 and fT3 levels) (group A_1:89) and overt hypothyroidism (TSH ≥ 10 µIU/ml and/ or abnormally low fT4 and fT3 levels) (group A_2:62). Patients were considered as hyperthyroid when serum TSH level was <0.34 µIU/ml with fT3 and/or fT4 above the specified reference ranges.

Reference range for serum FSH, LH and prolactin in follicular phase was 1-10 IU/L, 1.68-15 IU/L and 3.34-26.72ng/mL respectively. Values are expressed as mean ± SD. Statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, Illinois). We used unpaired‘t’ test to compare hormone levels between patients and controls.

3. Results

Serum LH, FSH levels were significantly lower and serum prolactin levels were significantly higher in patients with infertility and hypothyroidism (Table 1). Serum LH, FSH levels were significantly higher in infertile females with hyperthyroidism whereas serum prolactin levels were lower but not significantly in these patients (Table 1). Serum TSH was negatively correlated to LH and FSH and positively correlated to prolactin in patients with hypothyroidism (Table 2). Correlation between TSH and gonadotropins and prolactin was statistically significant in these patients. In patients with hyperthyroidism no significant correlation was found between TSH and serum gonadotropin levels (Table 3).

Table 1. Gonadotropin and prolactin levels in females with thyroid dysfunction as compared to controls (mean ± SD)

Hormone	Hypothyroidism	Hyperthyroidism	Controls
TSH	10.48 ± 6.08**	0.12 ± 0.08**	3.61 ± 0.9
Free T3	2.97 ± 0.64**	5.25 ± 0.98**	3.21 ± 0.04
Free T4	0.72 ± 0. 20**	1.58 ± 0.06**	0.94 ± 0.03
LH	4.93 ± 2.3**	20.24 ± 9.6**	8.98 ± 4.3
FSH	6.52 ± 4.28**	38.47 ± 26**	11.87 ± 4.5
Prolactin	41.95 ± 17.75**	15.49 ± 5.3	18.59 ± 12.0

** p value vs control <0.001; significant

Table 2. Correlation coefficient of thyroid function with serum gonadotropins and prolactin in hypothyroidism

Parameter	TSH		T3		T4	
	r value	p value	r value	p value	r value	p value
LH	-0.452	.000*	0.634	.000*	0.603	.000*
FSH	-0.462	.000*	0.562	.000*	0.543	.000*
Prolactin	0.710	.000*	-0.473	.000*	-0.446	.000*

*highly significant

Table 3. Correlation coefficient of thyroid function with serum gonadotropins and prolactin in hyperthyroidism

Parameter	TSH		T3		T4	
	r value	p value	r value	p value	r value	p value
LH	-0.119	.410	0.517	.000*	0.477	0.000*
FSH	0.100	.488	0.243	.089	.236	0.099
Prolactin	0.038	.792	0.165	.253	.223	0.120

*highly significant

4. Discussion

Thyroid disorders have a great impact on fertility in females. Fertility improves when euthyroidism is restored (3). It has been suggested that normal gonadotropin and thyroid function tests are necessary to achieve maximum fertilization rate and blastocyst development (10). Moreover, it has also been shown that serum TSH levels are significant predictor of fertilization failure in women undergoing IVF (11). This supports the importance of the role of thyroid hormones in oocyte physiology.

In our study females with hypothyroidism had significantly high serum prolactin levels as compared to controls. We found a significant positive correlation between serum TSH and prolactin levels and negative correlation between T_3, T_4 levels and prolactin.

Low serum levels of thyroxine (fT4) would decrease negative feedback on the hypothalamopituitary axis resulting in increased secretion of thyrotropin releasing hormone (TRH). TRH stimulates thyrotrophs as well as lactotrophs, thereby increasing the levels of both thyroid stimulating hormone (TSH) and prolactin (12).

Hyperprolactinemia causes dysovulation, increasing the chances of infertility because of inadequate corpus luteal progesterone secretion when levels are mildly elevated, and menstrual disturbances like oligomenorrhea or amenorrhea when levels of circulating prolactin are very high but the exact mechanisms by which prolactin influences the neuroendocrine axis are yet to be elucidated (13). It has been suggested that hyperprolactinemia leads to inhibition of gonadotrophin releasing hormone (GnRH) release pulsatility from the hypothalamus and subsequent inhibition of LH and FSH (14, 15). This might be the reason for decreased LH, FSH levels in these patients thus contributing further to infertility. Treatment with thyroxine has been shown to normalize prolactin levels and it also normalizes LH response to LHRH increasing the chances of spontaneous fertility (13, 16).

Thyrotoxicosis in women has been linked with reduced fertility but the mechanism for the same has not been elucidated clearly. We found that serum LH and FSH were very significantly high in these patients whereas serum prolactin levels were not significantly different as compared to controls. This was in corroboration with study done by Akande and colleagues and Pontikides et al (17, 18). Whereas study conducted by Zahringer et al found that FSH levels remain normal in thyrotoxic females (19). The mechanism for the increase in serum LH and FSH in hyperthyroid women remains unclear (20).

5. Conclusion

We suggest screening of thyroid hormone, in all the females with infertility. This can be useful in treating infertility at an early stage but further long-term prospective research is needed to reveal the benefit of treating thyroid dysfunction at an early stage.

References

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2008; 90: S60.
2. Dittrich R, Beckmanna MW, Oppelta PG, et al. Thyroid hormone receptors and reproduction. J Reprod Immunol. 2011; 90(1): 58-66.
3. Kris P, Brigitte V. Female infertility and the thyroid. Best Pract Res Clin Endocrin Metab. 2004; 18(2): 153-165.
4. Reh A, Grifo J, Danoff A. What is a normal thyroid-stimulating hormone (TSH) level? Effects of stricter TSH thresholds on pregnancy outcomes after in vitro fertilization. Fertil Steril. 2010; 94(7): 2920-2922.
5. Jones DD, May KE, Geraci SA. Subclinical thyroid disease. Am J Med. 2010; 123(6): 502-504.
6. Poppe K, Velkeniers B. Thyroid disorders in infertile women. Ann Endocrinol (Paris). 2003; 64(1): 45-50.
7. Zollner U, Lanig K, Steck T, et al. Assessment of endocrine status in patients undergoing in-vitro fertilization treatment. Is it necessary? Arch Gynecol Obstet. 2001; 265(1): 16-20.
8. Bergh T, Skarin G, Nillius SJ, et al. Pulsatile GnRH therapy d an alternative successful therapy for induction of ovulation in infertile normo- and hyperprolactinaemic amenorrhoeic women with pituitary tumours. Acta Endocrinologica. 1985; 110(4): 440-444.
9. Unuane D, Tournaye H, Velkeniers B, et al. Endocrine disorders and female infertility. Best Prac Res Clin Endocrin Metab. 2011; 25(6): 861-873.
10. Maruo T, Matsuo H, Mochizuki M. Thyroid hormone as a biological amplifier of differentiated trophoblast function in early pregnancy. Acta Endocrinologica (Copenhagen). 1991; 125(1): 58-66.
11. Cramer DW, Sluss PM, Powers RD, et al. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? J Assist Reprod Genet.2003; 20(6): 210-215.
12. Longcope C, Abend S, Braverman LE, et al. Androstenedione and estrone dynamics in hypothyroid women. J Clin Endocrin Metab. 1990; 70(4): 903-907.
13. Krassas GE. Thyroid disease and female reproduction. Fertil Steril. 2000; 74(6): 1063-1070.
14. Poppe K, Velkeniers B. Thyroid disorders in infertile women. Ann Endocrinol (Paris). 2003; 64(1): 45-50.
15. Zollner U, Lanig K, Steck T, et al. Assessment of endocrine status in patients undergoing in-vitro fertilization treatment. Is it necessary? Arch Gynecol Obstet. 2001; 265(1): 16-20.
16. Redmond GP. Thyroid dysfunction and women's reproductive health. Thyroid. 2004; 14(1):S5–S15.
17. Akande EO, Hockaday TD. Plasma luteinizing hormone levels in women with thyrotoxicosis. J Endocrinol. 1972; 65(9): 173–174.
18. Pontikides N, Kaltsas Th, Krassas GE. The hypothalamic-pituitary-gonadal axis in hyperthyroid female patients before and after treatment. J Endocrinol Invest. 1990; 13(2 Suppl): 203.
19. Zahringer S, Tomova A, Von Werder K, et al. The influence of hyperthyroidism on the hypothalamic-pituitary-gonadal axis. Exp Clin Endocrinol Diabetes 2000; 108(4): 282-289.
20. Krassas GE, Poppe K, Glinoer D. Thyroid Function and Human Reproductive Health Endocr Rev. 2010; 31(5): 702-755.