Original Research Paper

Volume-7 | Issue-11 | November-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Biochemistry

CORRELATION OF PROLACTIN WITH TSH AND FT4 IN INFERTILE FEMALES

Dr Madhurima Bora* Assistant Professor, Department of Biochemistry, Silchar Medical College, Silchar, Assam *Corresponding author

Dr Arpana Hazarika Associate Professor, Department of Physiology, Gauhati Medical College, Guwahati, Assam

ABSTRACT

Introduction: Infertility is defined as the failure of a couple to achieve conception (regardless of cause) after one year of unprotected and adequately timed intercourse. Hormonal disorders in females mainly relate to the aberrant dysfunction of hypothalamic pituitary ovarian axis.

Aim: To determine whether there is any association between Thyroid hormones and Prolactin in the infertile females.

Method and Materials: In this study 62 hyperprolactinaemic infertile females and 62 healthy fertile females were taken and Serum Prolactin, TSH and FT_4 were analysed in Access 2 immunoassay analyzer of Beckman Coulter following the principal of chemiluminescence.

Results: From the study it was found a significant increase of TSH level and decrease of FT_4 level in infertile hyperprolactinaemic females, when compared with the fertile female. In infertile females, the TSH level has a positive correlation and the FT_4 level has a negative correlation with Prolactin.

Conclusion: The Thyroid hormones and Prolactin estimation must be mandatory while investigating an infertile female.

KEYWORDS : Infertility, Prolactin, Thyroid stimulating hormone (TSH)

Introduction:

Infertility has become one of the major problems in our society. Infertility is defined as the failure of a couple to achieve conception (regardless of cause) after one year of unprotected and adequately timed intercourse (1). Infertility can be primary when the couple has never conceived despite exposure to unprotected sex of 2 years or secondary when the couple had a previous pregnancy but unable to go for second pregnancy. Infertility 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 (2). 40% of all cases of infertility are due to problems with the female partner and 30% are due to problems in male partner and the rest due to a cause which effects both the partners or to a cause which cannot be identified (3). The main causes leading to infertility in both males and females is stress and age related problems. The main causes in females are pelvic inflammatory diseases, endometriosis, polycystic ovarian disorders, premature ovarian failure, uterine fibroid and in males it is the poor semen quality. Many chemicals such as silicones, physical agents, chemical dusts, pesticides and volatile organic solvents also affect fertility. Even the weight of a women also plays an active role in fertility such that obesity causes an increase in estrogen production and affects fertility and too little fat causes insufficient estrogen production, menstrual irregularities with an ovulatory cycle. Hormonal disorders in females mainly relate to the aberrant dysfunction of hypothalamic pituitary ovarian axis. Thyroid dysfunction which is quite prevalent in the population affects many organs including male and female gonads interferes with human reproduction physiology which reduces the likelihood of pregnancy and adversely affects pregnancy outcome thus becoming relevant in the algorithm of production dysfunction (4). Pituitary hormones such as TSH, Prolactin or growth hormones may act synergistically with FSH and LH to enhance the entry of non-growing follicles into the growth phase (5). Morphological changes observed in the follicles in hypothyroidism can be a consequence of higher Prolactin production and may block both secretion and action of gonadotrophins (6,7) Free thyroid hormones (FT_4 and FT_3) concentration are independent of changes in the circulation and affinity of thyroid hormones- binding proteins and theoretically provide a more reliable means of diagnosing thyroid dysfunction than measurement of total hormone concentration(8). Prolactin is a single polypeptide having 198 amino acids secreted by the pituitary lactomorphic cells. The lactomorphs comprise 10% of the anterior pituitary cells in men and 20% in females. Secretion of Prolactin is under hypothalamic control and is unique because the main control of its secretion is inhibitory rather than stimulatory. Dopamine is believed to be the principal inhibitory factor that regulates Prolactin secretion. Other factors like vaso active inhibitory peptide (VIP) and Thyroid releasing hormone (TRH) cause an increase in Prolactin secretion(9). In fact TRH in addition to increasing TSH cause to rise Prolactin level(10). The main function of Prolactin is to increase breast development during pregnancy and to induce lactation. It also has a role in complex process controlling the gonadal function. Its secretion is pulsatile, it increases with sleep, stress, pregnancy and chest wall stimulation or tumours(11). Hyperprolactaemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering ovulation(12,13). This disorder has been implicated in menstrual and ovulatory dysfunction like amenorrhoea, oligomennorhoea, anovulation, inadequate, inadequate corpus luteal phase and galatorrhoea(14,15). Different increase level of serum Prolactin has been reported in 30% of patients with primary hypothyroidism (16). Even in the absence of hyperprolactinaemia, hypothyroidism can contribute to infertility. This is because thyroid hormones are necessary for maximum production of progesterone and estradiol(17).

Aim of the Study :

1) To assess the levels of serum Prolactin and thyroid hormones (TSH and FT_4) in infertile females
2) To determine if there is any association between thyroid hormones (TSH and FT4) levels and Prolactin in our population in Barak valley of Assam, India

Materials and Method :

The study was conducted in Silchar Medical College, Silchar, Assam , India

Study design : It is a hospital based case control study.

Study population :
Women in fertility age group (20 -40 yrs) attending infertility clinic of obstetrics and gynaecology department of Silchar Medical College

Sample size :
124 patients out of which 62 are infertile patients with hyperprolacintaemia and 62 healthy fertile individuals with at least one child.

Study duration : From January 2017 to June 2017 (six months)

Inclusion criteria :
Diagnosed infertile cases between 20-40 yrs
Duration of Marriage should be more than one year

Exclusion criteria:
Male factor infertility
Congenital anomaly of urogenital tract
Organic lesions$_4$

Thyroid surgery
On thyroid medication

Methodology:
Detail history and written consent was taken from the patient before recruiting them.

Procedure:
With all aseptic and antiseptic measures 5 ml of blood is collected from the central median cubital vein from both control and experimental groups. The blood is immediately transferred into labeled clotted vials after removing the needle very slowly to prevent hemolysis. Then the blood is allowed to clot for 30 to 45 minutes after putting the stopper to the vial. The clot is rimmed and centrifuged for 5 minutes at 3000 rpm in a clinical centrifuge machine. All the parameters –Serum Prolactin, TSH and FT_4 were analysed in Access 2 immunoassay analyzer of Beckman Coulter following the principal of chemiluminescence.

Statistical analysis:
The results were expressed as mean ± standard deviation. The paired sample t-test was used to determine whether there exist a significance difference between the means of the two groups (i.e healthy fertile women having at least one offspring and hyperprolactinaemic infertile women) taken from two populations with unknown variance.

For testing normality assumption and for assessing whether our collected sample datasets were approximately follow normal distribution, analysis of normality was done (which typically combines normal probability plots with hypothesis tests). The association between variables was assessed by pearson's bivariate coefficient of correlation. Simple linear regression was employed to get a linear representation of our dataset between the predictor and response and to fit an approximate trend line. Testing the null hypothesis H0: $\phi = 1$ versus the alternative hypothesis H1: $\phi \neq 1$ was considered to test of significance of the parameters based on the 'P' value and a P value ≤ 0.05 was considered statistically significant. All the statistical analyses were performed using the MATLAB R2012a and in MS-excel.

Results:
In this study, 124 patients were taken out of which 62 infertile females (hyperprolectinaemic) were attending infertility clinic of obstetrics and gynaecology department of Silchar Medical College, Silchar and 62 healthy fertile patients who have at least one child.

Results of the study were given in Table 1 and Table 2. The basic statistics of Prolactin, TSH and FT_4 of healthy fertile females and infertile hyperprolactinaemic females were plotted in Figure 1, Figure 3 and Figure 5 respectively. The plots display the distribution of the samples around the medians and their medians were different at default 5% significance. In Figure 2 and Figure 4, both the samples (i.e healthy fertile females and infertile females) scatter approximately follow straight lines, through the first and third quartiles of the samples indicating approximate normal distribution. The infertile female group showed a deviation to the right from the normality. In Figure 6, though it followed normal distribution but there was a shift of the infertile group to the left side of the normal fertile group. We had done the students't' test and compare our test statistics with a critical "t_α" value (as presented in the Table 2). Thus we have concluded that there exist significant statistical differences of mean between the two groups and so it was unlikely that our results occurred by chance and the null hypothesis was rejected at the acceptable 5% significance level.

Correlation coefficient was calculated between Prolactin and TSH levels in infertile females in Figure 7 and between Prolactin and FT_4 in infertile patients in Figure 8. It was found that TSH (dependent variable) has a positive correlation with Prolactin (independent variable) (r = 0.662, p = 4.82E-09) and FT_4 (dependent variable) has a negative correlation with Prolactin (r = - 0.679, p = 1.31E-09); negative sign indicates that there exist a decreasing trend of response variable FT_4 with the increase of the predictor variable Prolactin.

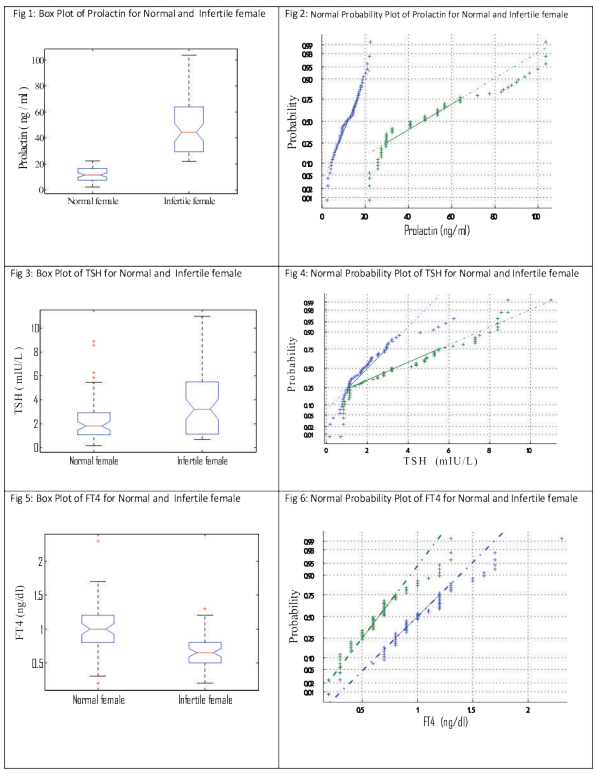
From the test of significance of the regression parameters, we accept the alternate hypothesis as P values of all the regression coefficients were < 0.001, which ensures that the coefficients were not equal to zero and has a significant role in linear representation our sample datasets and thus to determine the values of TSH and FT_4 through Prolactin as obtained from simple regression equations as presented in the Figure 7 & Figure 8 respectively.

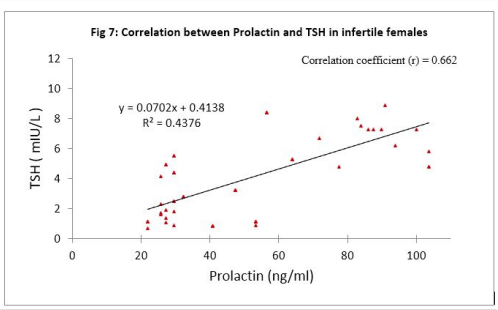
Table 1: Basic statistics of Prolactin, TSH and FT_4 in normal and infertile females

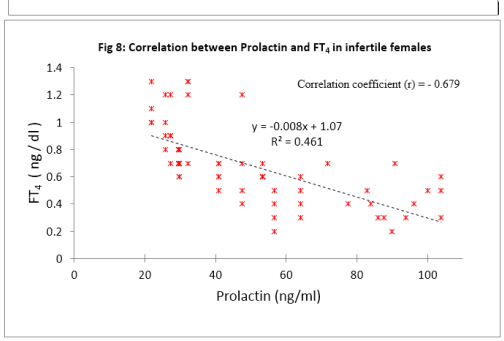
Basic Statistics	Prolactin		TSH		Ft_4	
	normal	Infertile	normal	Infertile	normal	infertile
Mean±-SD	11.74± 5.50	50.61± 25.34	2.26± 1.70	3.97± 2.69	1.05± 0.38	0.68± 0.29
Median	11.31	44.16	1.81	3.21	1.00	0.65
S.E	0.70	3.22	0.23	0.34	0.05	0.04
Minimum	2.15	21.83	0.16	0.70	0.20	0.20
Maximum	22.29	103.70	8.90	11.00	2.30	1.30

Table 2: P and t values of infertile females as compared with fertile females

P and t values	Prolactin	TSH	FT4
P	<0.001	<0.001	<0.001
t	-10.12	-4.01	6.14
t_α (critical at α= 5%, df=60)	2.00	2.00	2.00







Discussion:

In this study both the fertile and infertile groups fall under the reproductive age group (20 - 40 yrs). Table 1 shows significant increase in serum TSH and Prolactin levels in infertile female group when compared with the control fertile group. The hypothalamus through the release of gonadotropin releasing hormones controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body. So any change in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence hormonal abnormalities occur. Hormonal anomalies do not produce enough follicles that affect ovulation include hyperthyroidism, hypothyroidism, polycystic ovarian disease and hyperprolactinaemia(18). The mean serum TSH concentration of the hyperprolactinaemic infertile females was significantly higher ($P<0.001$) than those of the control fertile group. This is similar to observations with study by Sharma et al (19) and Turankar et al (20), A significant positive correlation between TSH and Prolactin levels was seen in Figure 7, ($r = 0.662$, $p = 4.82E-09$). This supports the finding of Goswami et al(17). Then in Figure 8 a negative correlation between FT_4 and Prolactin ($r = - 0.679$, $p = 1.31E-09$) was observed which clearly signifies thyroid hypofunction. Thyroid hypofunction is characterized by low serum levels of T_4 because of this low level there is increase in secretion of thyrotropin releasing hormone (TRH) in some individuals. TRH increases the levels of both Prolactin and TSH by stimulating the thyrotrophs and lactotrophs(21). In this study the relative higher incidence of TSH values in hyperprolactinaemic infertile patients than the fertile group shows that there is a tendency of hyperprolactinaemic infertile patients to have thyroid insufficiency and vice versa. Evidence from experimental and clinical studies have suggested a close relationship between the hypothalamic-pituitary-ovarian axis (HPO) and the hypothalamo-pituitary-thyroid axis (HPT) (20). This is because the specific thyroid hormone receptors at the ovarian level may regulate the influence of oestrogens as well as reproductive function at the higher levels of the HPT axis thereby integrating the reciprocal relationship between these two major endocrine axis (22). There is decrease of FT_4 in the infertile group when compared to the control fertile group. This makes it more prominent that these patients are having hypothyroidism as the levels of FT_4 are inversely proportional to TSH which has an increasing trend with increased Prolactin levels. The negative feedback on the hypothalamo-pituitary axis results in increased secretion of TRH which in turn stimulates thyrotrophs and lactotrophs thereby increasing the levels of both TSH and Prolactin. Hyperprolactinaemia resulting from long standing primary hypothyroidism has been implicated in ovulatory dysfunctions ranging from inadequate corpus luteal progesterone secretion when mildly elevated to oligomenorrhoea or amenorrhoea when circulating Prolactin levels are high it is demonstrated by menorrhagia or oligomenorrhoea, pregnancy, loss and /or infertility(23,24.25)

Conclusion :

From the study, it is seen that a correlation exist between the thyroid hormones and Prolactin in infertile women as the secretion of both thyroid hormones and Prolactin follow hypothalamo-pituitary axis. So it should be mandatory to test both thyroid hormones and Prolactin levels while investigating an infertile woman.

References :

1) Evers MC, The infertile couple, Am Fam Physician(2002);54(3):1001-10
2) Wright KL, Defining what infertility means for clinicians and clients, Network, (2003);23(2):4-6
3) Fritz MA, Speroff L, Clinical gynaecologic endocrinology and infertility,12th edition New York, Blackwell 2010
4) Warg C and Crapo LM, The epidemiology of thyroid disease and implication for screening, Endocrinology and metabolism clinics of North America,26, 189-218 (1992)
5) Micinsk P,Wielgus E, Wojeieszyn M, and Pawlicki K (2006) Abnormal ovarian reserve test reflects thyroid dysfunction, Pol J Gyn Invest; 9(1): 30-4
6) Armada-Dias L,Carvalho JJ, Breitenbach MM, Franci CR, and Maura EG (2001) Is the infertility in hypothyroidism mainly due to ovarian and pituitary functional changes? Braz J Med Biol Res; 34(9) 1209-15
7) Rahman D, Fatima P, Banu J, (2008) Thyroid disorder in female subfertility JMCTA, 19(2); 146-50
8) Demers LM,Pituitary functions, Tietz fundamentals of clinical chemistry ,5th edition(2001)pg 822-838
9) Surks MI, Ortiz E, Daniels GH, et al, Subclinical thyroid disease scientific review and guidelines for diagnosing and management JAMA, 2004; 14 228-38
10) Hollowell JG, Stachling NW, Flanders WD, 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: 489-99
11) Nilsson LA, Roop C, Kens B, Billg H, Ling C, Prolactin suppresses malonyl CoA concentration in human adipose tissue, Hom Metab, Res (2009); 4(10):747-5
12) Poppe K, Velkniers B, Thyroid disorders in infertile women, Ann endocrinol (Paris) 2003; 64(1) 45-50
13) Zollner U, Lanig K, Steek T, Diell J, ASSessment of endocrine status in patients undergoing in vitro fertilization treatment, Is it necessary, Arch gynaecol Obste 2001; 265(1) 16-20
14) Mishra R, Baveja R, Gupta V, Prolactin level in infertility with menstrual irregularities, J. obstet Gynaecol India 2002; 52: 40-3
15) del Pazo E, Wyrs H, Tollis G, Alcarliz J, Campora A,Natrokin F, Prolactin and deficient luteal function, Obst. Gynaecol 1979; 53(3) 1282-6
16) Cooper D S, Halpern R, Wood L C, Levin AA, Ridgway EC, Thyroxine therapy in subclinical hypothyroidism A double blind placebo controlled trial, Am Inter Med, 1984 (10):18-24
17) Goswami B, Patel S, Chatterjee M, Koner B C, Saxena A, A correlation of Prolactin and thyroid hormone concentration with menstrual patterns in infertile women, J Reprod Inferti, 2009; 10(3):207-12
18) Legro RS(2007) A 27 year old women with a diagnosis of polycystic ovary syndrome JAMA,297(5):509-519
19) Sharm P, Suvarna P, Nitin T,Female infertility and its correlation with serum Prolactin and TSH concentration an unmatched case control study, J Pharm Biomed SCi2003;30(30):902-07
20) Turankar S, Sonone K, Turankar A, Hyperprolactinaemia and its comparison with hypothyroidism in primary infertile women, J Clin Diag Res. 2013; 7(5):794-96
21) Emokpae MA, Osadolor HB, Omole-Ohonse A. Subclinical hypothyroidism in infertile Nigerian women wit hyperprolactinaemia. Nig J Physol Sci 2011;26:35-38
22) Saha S, The female reproductive system and the hypothalamic-pituitary thyroid axis(internet) 2012, (cited 2014 Aug 21) Available from http//pharmaceuticalintelligence.com/2012/12/11/the female reproductive system and the hypothalamic-pituitary-thyroid axis,
23) Sharma B, Kumar A, Singh CM and Kansal R, (2012) Significance of thyroid profile (serum T3,T4 andTSH) in infertile women. Ind J common health;24(2):144-151
24) Krassas GE(2000) Thyroid disease and female reproduction Fertil Steril;74(6):1063-70
25) Krassas GE, Pontikidis N, Kaltas T, Papadopoulou P, Paukovie J, Paunkovic N, Duntas Lh.(1999) Disturbances of menstruation in hypothyroidism, Clin Endocrinol(0xf), 2(3) 370-385