Correlation of Thyroid Hormones with FSH, LH and Prolactin in Infertility in the Reproductive Age Group Women

Santosh Fupare[1,*], Bina M. Gadhiya[2], Rajesh K. Jambhulkar[3], Archana Tale[4]

[1]Assistant Professor, Department of Biochemistry, Seth G.S. Medical College and KEM Hospital, Maharashtra,
[2]Associate Professor, Department of Biochemistry, Government Medical College, Aurangabad, Maharashtra,
[3]Assistant Professor, Department of Biochemistry, People's College of Medical Sciences and Research, Bhopal, Madhya Pradesh, [4]Junior Resident, Department of Anatomy, GMC, Aurangabad, Maharashtra

***Corresponding Author:**
E-mail: drsantoshfupare@rediffmail.com

ABSTRACT

Introduction: *The prevalence of infertility is estimated to be between 12 and 14%. It thus represents a common condition, with important medical, economic and psychological implications. Proper evaluation of these disorders involves a multidimensional diagnostic approach. The present study was carried out to correlate thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women.*

Aim: *The aim of this research work was to correlate thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women.*

Material and Methods: *Total 120 infertile women, and 80 normal fertile women volunteers were selected on OPD basis between age group of 19 to 45 years. Out of 120 infertile women, 80 were of primary infertility and 40 of secondary infertility. They were screened for thyroid hormone status by Chemiluminescence Immunoassay (CLIA).*

Result and Discussion: *Prolactin and TSH were positively correlated with each other. They were also negatively correlated with LH, FSH & T3 in infertile groups. Therefore we can say that hyperprolactinemia & hypothyroidism plays key role in etiopathogenesis of infertility.*

Long standing hypothyroidism may develop ovulatory dysfunction, and hyperprolactinemia. So identifying and treating hypothyroidism at an earlier stage before the appearance of ovulatory dysfunction and hyperprolactinemia, can have potentially great preventive value. So TSH screening of all females of early reproductive age group should be done so as to detect subclinical thyroid problem and to prevent infertility risk.

Key Words: *Infertility, Thyroid hormones, FSH, LH, Prolactin, Chemiluminescence, Hypothyroidism etc*

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-6377.2015.00005.2

INTRODUCTION

Hormonal disorders of female reproductive system are comprised of a number of problems resulting from dysfunction of hypo-thalamic-pituitary ovarian axis. These relatively common disorders often lead to infertility[1].

Parenthood is undeniably one of the most universally desired goals in adulthood, and most people have life plans that include children. However, not all couples who desire a pregnancy will achieve one spontaneously and a proportion of couples will need medical help to resolve underlying fertility problems. Infertility has been recognized as a public health issue worldwide[2].

Many people may be infertile during their reproductive years. They may be unaware of this infertility. Many parameters are outlined for the cause of infertility like age, lifestyle and physical problems etc.

The infertility problem is more common phenomenon among the women now days and has increased over past 30 years[3].

The prevalence of infertility is estimated to be between 12 and 14%. It thus represents a common condition, with important medical, economic and psychological implications[4]. Proper evaluation of these disorders involves a multidimensional diagnostic approach.

Pituitary hormones such as TSH, prolactin or growth hormone 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 that may block both secretion and action of gonadotropins[6]. Adequate thyroid supplementation also restores prolactin levels as well and normalizes ovulatory function[7]. 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[8]. Clinical and experimental studies have suggested a close relationship between the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-ovarian axis.

FSH stimulates follicle development in the ovaries and is often used as a gauge of ovarian function. Elevated

FSH level indicate poor follicle development and consequently, anovulatory cycles. Reduced levels of FSH may indicate hyperprolactinaemia[9].

LH triggers the release of the ovum from the ovary – the LH surge at around day 12 leads to ovulation within 48 hours. Elevated LH levels can indicate ovarian dysfunction. Reduced levels of LH may indicate hyperprolactinaemia[9].

There is a relationship between gonadotropins and thyroid hormones but it was found that very little work has been done about the relationship of thyroid hormones and serum gonadotropins. Hence we were conducted this study "correlation of thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women."

The aims and objectives of present study are as follows:

Aim of this study was correlation of thyroid hormones with FSH, LH and prolactin in infertility in the reproductive age group women.

Specific Objectives

1. To correlate between thyroid hormones, serum prolactin, LH and FSH in infertile women.
2. To study comparison of these hormonal levels in fertile and infertile women.

MATERIAL AND METHODS

Study Design: Cross sectional Study

Time Period: 2010-2012

Institute: Department of Biochemistry, Government Medical College, Aurangabad

Age Group: 19-45 years

After written and informed consent, total 120 infertile women, and 80 normal fertile women volunteers were selected on OPD basis between age group of 19 to 45 years. Out of 120 infertile women, 80 were of primary infertility and 40 of secondary infertility.

Participants were selected on the basis of detailed history, clinical examination and laboratory investigations. Detailed history of participants including age, menstrual history, obstetric history, history of any medications, addictions, was taken.

Inclusion Criteria:

1. Infertile women age between 19 to 45 years.
2. Normal fertile women age between 19 to 45 years.

Exclusion Criteria:

1. Male factor infertility.
2. Patient who received medication that could alter TFT. (amiodarone an phenytoin excluding β-blockers, heparin & dopamine)
3. Amongst the female factors were tubal factor, any congenital anomaly of the urogenital tract, or any obvious organic lesion.
4. Any history of thyroid disease or previous thyroid surgery.

Biochemical Investigations:

After written informed consent, 12 hour fasting venous blood samples were collected from all participants in there early follicular phase of menstrual cycle i.e. between days 3^{th} to 5^{th} in plane bulbs. Serum was separated after 1 hour by centrifugation at 3000 rpm for 10 minutes, and was tested for following parameters.

1. Serum FT_3
2. Serum FT_4
3. Serum TSH
4. Serum FSH
5. Serum LH
6. Serum Prolactin

METHOD

Quantitative estimation of all hormones done by Chemiluminescence Immunoassay (CLIA) using Acculite CLIA micro wells.

Assay kits from Monobind INC., Lake Forest, CA 92630, USA.

RESULTS

Table 1: Showing number of study subjects and their groups

Group	Subjects	Number (n)
I	Infertile women (cases)	120
II	Normal fertile women (control)	80

Table 2: Showing number of subgroups in group I

Group	Subjects	Number (n)
IA	Primary infertile women	80
IB	Secondary infertile women	40

Table 3: The mean age distribution of subjects

Variable	Group IA n= 80	Group IB n= 40	Group II (Control) n= 80
Age	23.525 ± 2.48	27.575 ± 1.94	27 ± 2.12

Table 4: Hormonal status in the Cases and Controls

	CASES (n=120)			CONTROLS (n=80)		
	Euthyroid (n=93)	**Hyperthyroid (n=5)**	**Hypothyroid (n=22)**	**Euthyroid (n=68)**	**Hyperthyroid (n=6)**	**Hypothyroid (n=6)**
FT3 (pg/ml)	2.34±0.8	5.2±0.55	1.1±0.2	2.8±0.23	5.05±0.31	1.01±0.14
FT4 (ng/ml)	1.5±0.4	3.2±0.64	0.66±0.07	1.4±0.89	3.1±0.33	0.45±0.11
TSH (µIU/L)	3.9±1.6*	0.24±0.05	8.72±0.79**	3.36±0.8	0.17±0.4	6.86±0.45
Prolactin (ng/ml)	30.9±17***	16.01±1.06**	77±9***	13.6±6.0 9	8.1±3.2	29.7±2.01
LH (IU/L)	6.02±2.7***	6.5±1.29**	3.34±1.0***	8.2±2.04	7.39±0.85	9.9±2
FSH (IU/L)	4.1±2.64**	3.6±0.75**	3.44±2.08***	6.7±1.6	6.19±1.01	10.38±1.3

***P<0.5, **p<0.01 and ***p<0.001** in comparing the distributions to the respective group in controls.

Thyroid function status in the study population is presented in table 4. Cases and control further divided in Euthyroid, Hyperthyroid & hypothyroid according to their thyroid hormones status. Most of the infertile women 93/120 **(77.5%)** and control 68/80 **(85%)** were **euthyroid**. The prevalence of **hyperthyroidism** in the cases and the controls were 5/120 **(4%)** and 6/80 **(7.5%)**, respectively.

Hypothyroidism was seen in 22/120 **(18%)** of the infertile women whereas in the control group it was found to be 6/80 **(7.5%)**. The crude prevalence of hypothyroidism was higher when compared to hyperthyroidism in the infertile group.

Significantly higher serum TSH levels were noted in the infertile cases with euthyroid ($p<0.5$) and hypothyroidism ($p<0.01$) when their distributions were compared to their respective control groups. The rise in serum FT4 and FT3 in the infertile group with hyperthyroidism was found to be non-significant as compared to the control group with hyperthyroidism.

The mean serum prolactin concentration in the infertile cases with euthyroid was significantly higher ($p<0.001$) than the control group with euthyroid. The infertile women with hypothyroidism had significantly higher prolactin levels than the other three groups (the controls and the infertile subjects with euthyroid and hyperthyroidism) ($p<0.001$).

There is also higher level of prolactin in hypothyroid control as compared to euthyroid and hyperthyroid control.

Table 5: Hyperprolactinemia and Hypothyroidism in study groups:

Parameter	Control	Primary Infertility	Sec. Infertility
Hyperprolactinemia	6	44	10
Hypothyroidism	6	13	9

Serum prolactin levels > 25ng/ml. (Ref. range: 2 – 25) were observed in

- **6/80** participants in control (**7.5%**),
- **44/80** participants in primary infertile (**55%**) and
- **10/40** participants in sec. infertile (**25%**)

Serum TSH levels > 6.16 µlU/ml. (Ref. range: 0.39 – 6.16) were observed in

- **6/80** participants in control (**7.5%**),
- **13/80** participants in primary infertile (**16.2%**) and
- **9/40** participants in sec. infertile (**22.5%**)

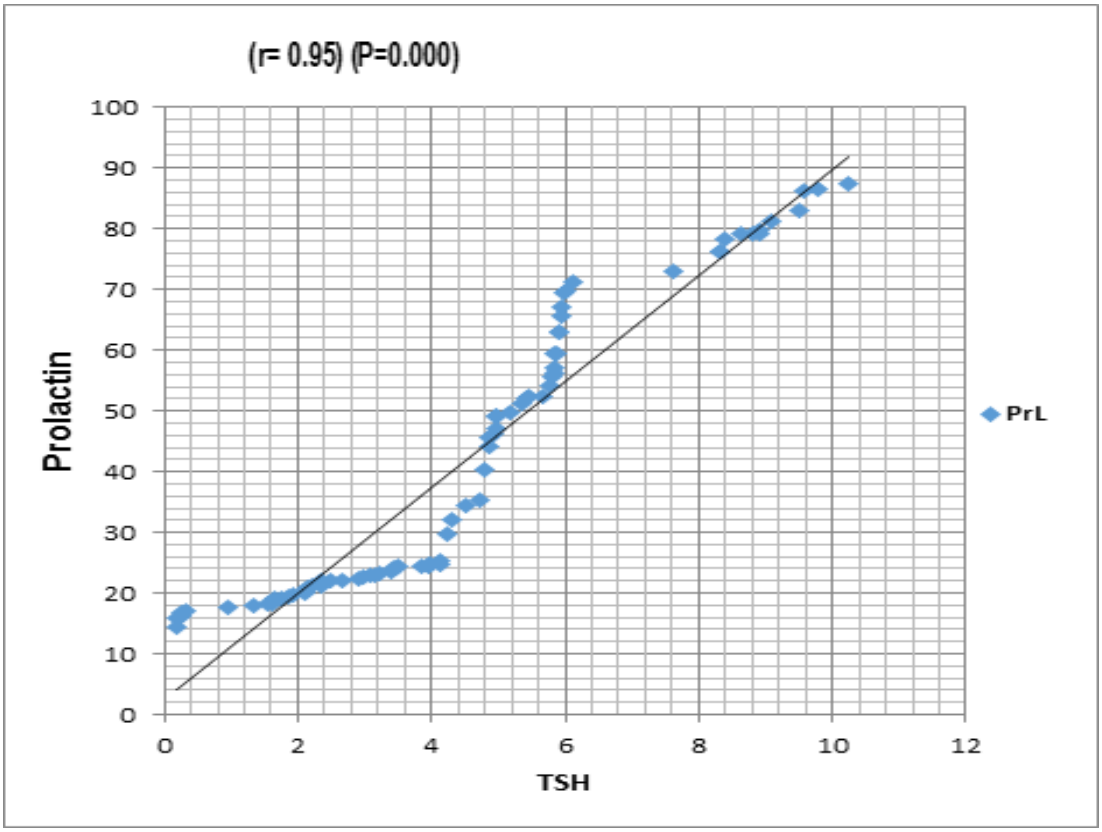
Out of 54 hyperprolactinemic infertile women 22 are hypothyroid therefore incidence of hypothyroidism in hyperprolactinemic infertile women is 40.7%.

Table 6: correlation coefficients (r value) in Primary infertility

	TSH	T4	T3	FSH	LH
Prolactin	r= **0.95*** P= **0.00**	-0.59 7.8	-0.68 3.5	-0.20 0.07	-0.62 6.7
LH	r= -0.60 P= 3.2	**0.18*** **0.002**	**0.21*** **0.000**	**0.45*** **0.000**	
FSH	r= -0.14 P= 0.203	0.017 0.87	-0.05 0.60		
FT3	r= -0.76 P= 2.7	0.78 4.84			
FT4	r= -0.69 P= 9.01				

Prolactin is negatively correlated with all parameters except TSH which shows positive correlation.
Prolactin and **TSH** shows strong positive correlation with each other. **(r= 0.95) (P=0.000). TSH** also shows negative correlation with all parameters.
LH show positive correlation with **FT3** and **FT4. LH** also shows strong positive correlation with **FSH (r=0.45) (P=0.00)**.

Graph 1: Correlation of Prolactin and TSH in primary infertility



DISCUSSION

The current study was designed to correlate thyroid status in infertile women and its correlation with serum prolactin, LH & FSH. The individuals were divided in 2 groups according to fertility i.e. Group I Infertile women (cases), Group II Normal healthy fertile women (controls); Cases are further sub classified as Group IA (Primary infertile women) and Group IB (secondary infertile women).

It is well known that in both sexes thyroid hormones influence sexual development and reproductive function. Hypothyroidism from infancy, if untreated, leads to sexual immaturity and hypothyroidism beginning before puberty causes a delay in onset of puberty followed by anovulatory cycles. It is stated in different textbooks that in adult women, hypothyroidism results in changes in cycle length and amount of bleeding.
Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect

pregnancy outcome. Data on the relationship between thyroid disorders and infertility remain scarce and the association with a particular cause of infertility has not been thoroughly analyzed[11].

The increase in prolactin secretion can be physiological e.g. during pregnancy and lactation or pathological due to hypothalamic and pituitary diseases, or it can be iatrogenic. Hyperprolactinemia induces suppression of the hypothalamic-pituitary-gonadal axis and resistance of the ovary to gonadotropin action, which results in amenorrhea and lack of ovulation.

Serum Prolactin & Thyroid profile

1. Serum levels of Prolactin and TSH increased in infertile women as compared to control, the differences among three groups being highly significant (P< 0.001).
2. Serum Prolactin levels were found to be strongly correlated with TSH levels in primary infertile women and Secondary infertile women (r= 0.95 and 0.74 respectively) and this correlation was statistically significant (P< 0.001).
3. As per the study, we observed a greater percentage of infertile women with hypothyroidism exhibiting hyperprolactinemia (40.7%).

These findings in our study strongly correlate with the findings of study by **Goswami Binita et al (2009)[1]**, they found 46.1% infertile women with hypothyroidism had hyperprolactinemia.

Kumkum *et al* (2006)[10], in their study incidence of hypothyroidism in hyperprolactinemic women was 25.50% (13/51). So, a positive correlation of 1:4 was found between hypothyroidism and hyperprolactinemia.

Affia Tasneem et al (2011)[11], in their study measured Serum Prolactin and TSH levels in 1365 patients (46 males, 1319 females). They found 33% hypothyroid in hyperprolactinemic patients.

Mechanism whereby hypothyroidism associate with hyperprolactinemia can be as follows:-

In hypothyroidism there is increase TSH and Prolactin levels and produce pituitary enlargement, these alterations are mainly produced by the high levels of TRH induced by the decreased negative feedback of thyroid hormones at the hypothalamic-pituitary level. TRH stimulates the secretion of both TSH and Prolactin producing hypertrophy and hyperplasia of TSH and Prolactin secreting cells. In hypothyroidism the number and sensitivity of TRH receptors increases in the thyrotrope and the lactotrope. TSH and Prolactin responses to TRH are also increased[12].

It may be postulated that hypothalamic-pituitary-thyroid axis in such infertile women is less sensitive and they had compensated thyroid hormone profile with tissue hypothyroidism. Such thyroid under-function can affect female reproductive physiology indirectly in a number of ways:

1. Altering the pituitary ovarian axis.
2. Decreasing the binding activity of sex hormone binding globulin (SHBG) resulting in increased free testosterone and estradiol.
3. Decreasing the metabolic clearance of androstenedione and estrone.
4. It also increases TRH levels resulting in increased prolactin levels.
5. A delayed LH response to LH-releasing hormone.

Generally measurement of serum TSH in infertile women is employed for detection of hypothyroidism. TSH is an important hormone to access thyroid function but its normal range (usually 0.3-6.0 µIU/L) is wide. A limitation with its laboratory determination is that it cannot detect tissue hypothyroidism. Recent laboratory guidelines from the National Academy of Clinical Biochemistry indicate that more than 95% of normal individuals have TSH level below 2.5 µIU/[80]. The remainder, those with higher values is likely to have Hashimoto thyroiditis or other causes of elevated TSH.

Concluding points about relationship between Prolactin & Thyroid profile:

- There was a strong positive correlation between Prolactin and TSH levels and the correlation was statistically significant. (P< 0.001). Therefore hypothyroidism can be suggested as a surrogate marker of hyperprolactinemia.
- Prolactin showed negative correlation with FT3 & FT4 levels in infertility.

LH and FSH

In our study serum LH & FSH was decreased in infertile women as compared to control, the differences among three groups being highly significant (P< 0.001). LH & FSH both are negatively correlated with prolactin.

K. Mohan and Mazher Sultana (2010)[13], in their study of 70 women, found lower level of serum FSH in infertile women were when compared to control groups, difference being statistically significant (P<0.001). Serum LH concentration was lower in the infertile group than in the control group(P<0.001).

Azima Kalsum, Samina Jalali (2002)[14], in their study shows a significant decrease in serum LH in follicular, ovulatory and luteal phase in hyperprolactinemic women having primary and secondary infertility. Significantly (P<0.05) low serum FSH levels were observed in ovulatory phase in women reported with primary infertility. Similarly significant (P<0.05) decrease in serum FSH in luteal phase in hyperprolactinemic women reported with secondary infertility was observed.

Yamaguchi et al (1991)[15], found decreased LH secretion in nocturnal hyperprolactinemic women.

Mc Neilly A.S (1987)[16], showed similar association between increased level of prolactin and a reduction in both LH and FSH during infertility in women with pathological hyperprolactinemia.

From the present study we observed proportional increase in TSH and serum Prolactin in relation with

decreasing T3, T4, LH and FSH in infertile women. There was significant positive correlation of Prolactin with TSH. LH & FSH were decreased with increasing Prolactin.

Hyperprolactinemia resulting from longstanding primary hypothyroidism has been implicated in ovulatory dysfunctions ranging from inadequate corpus luteal progesterone secretion when mildly elevated, to oligomenorrhoea or amenorrhea when circulating prolactin levels are high. Amenorrhea occurs in hypothyroidism due to hyperprolactinemia resulting from a defect in the positive feedback of estrogen on LH, and because of LH and FSH suppression. Our study revealed a significant association between abnormal menstrual patterns, with hyperprolactinemia & hypothyroidism in the infertile group ($p<0.001$).

For these reasons, TSH and prolactin are commonly-ordered clinical tests in evaluating infertile women.

We included only 80 controls in our study as compared to 120 cases due to the stringent inclusion criteria and non-compliance, as the study has been a hospital-based one due to the difficulties in recruiting counter parting controls. To avoid the slightest traces of selection bias, the data should be extrapolated to the general population with care. For a better calculation of the intended prevalence, a population-based study may be conducted. As it was a cross sectional study, we cannot infer conclusions about cause and effect relationship between infertility and hypothyroidism as well as hyperprolactinemia.

All above findings need to be ascertained in the larger and well systematized with large number of control subjects (volunteers) and long follow up duration are necessary to validate the variation in TSH and prolactin levels and to clarify the etiology of the higher prevalence of hyperprolactinemia in hypothyroidism for better management of infertility cases.

This study may be extended as prospective follow up study by giving thyroxin supplement to all infertile women with hypothyroidism and hyperprolactinemia.

Thyroid function test and especially TSH is recommended for each hyperprolactinemic patient, to identify patients with hyperprolactinemia which is caused by hypothyroidism. Hypothyroidism in females, maternal hypothyroidism and sub-clinical hypothyroidism, should be extensively studied as secondary causes of hyperprolactinemia. Moreover some studies should address iodine deficiency disorder (IDD) and hypothyroidism and their relations to infertility.

SUMMARY AND CONCLUSION

The present study was carried out in 200 women classified according to fertility in normal fertile women (control), primary infertile women and secondary infertile women. The concept behind our work was to evaluate thyroid profile, prolactin, LH and FSH in all participants and to correlate these parameters with each other.

Prolactin and TSH were positively correlated with each other. They were also negatively correlated with LH, FSH & T3 in infertile groups. Therefore we can say that hyperprolactinemia & hypothyroidism plays key role in etiopathogenesis of infertility.

Considering primary and secondary infertility both had higher levels of serum prolactin & TSH as compared to control. Prolactin is significantly high in primary infertility as compared to secondary infertility while TSH values were slightly high in secondary infertility. LH, FSH, T3 & T4 values were low in infertile as compared to fertile, but among primary and secondary infertility their values not differ.

Both hypothyroidism and hyperprolactinemia may result in menstrual disorders. Oligomenorrhoea was most common in infertile women. Hypothyroidism is commonly associated with hyperprolactinemia and such patients exhibit ovulatory failure. Hence, assessment of serum TSH and prolactin levels are mandatory in the work up of all infertile women, especially those presenting with menstrual irregularities.

Although hypothyroid individuals tend to be hyperprolactinemic, and causes infertility, the most fundamental fact is that, not all infertile women are hypothyroid, nor do they all have hyperprolactinemia.

So the basic approach should be to identify those hypothyroid individuals who have hyperprolactinemia and are at greatest risk for the development of infertility. Those infertile women with normal levels of thyroid hormones may not necessarily indicate the true status of thyroid hormones in the body. All those infertile women with concurrent normal levels of thyroid hormones may still be having subclinical thyroid problem which may be responsible for infertility.

Long standing hypothyroidism may develop ovulatory dysfunction, and hyperprolactinemia. So identifying and treating hypothyroidism at an earlier stage before the appearance of ovulatory dysfunction and hyperprolactinemia, can have potentially great preventive value. So TSH screening of all females of early reproductive age group should be done so as to detect subclinical thyroid problem and to prevent infertility risk.

REFERENCES

1. Goswami B., Patel S., Chaterjee M., Koner B.C., Saxena A. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J Reprod Infertil. 2009;10(3):207-12.
2. Jacky B., Laura B., John A., Collins and Karl G.N. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Human Reproduction 2007;22,(6) 1506–1512
3. Stephen E.H., Chandra A. Use of infertility services in the United States: 1995. Fam Plann Perspect (2000) 32:132.
4. Nasima A., Sufi A. H. Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh

perspective after universal salt iodination. The Internet Journal of Endocrinology 2009; 5(1):about 8 p
5. Micińsk P., Wielgus E., Wojcieszyn M., Pawlicki K. Abnormal ovarian reserve test reflects thyroid dysfunction. Pol J Gyn Invest. 2006;9(1):30-4.
6. Armada-Dias L., Carvalho J.J., Breitenbach M.M., Franci C.R., Moura E.G. Is the infertility in hypothy-roidism mainly due to ovarian or pituitary functional changes? Braz J Med Biol Res. 2001;34 (9):1209-15.
7. Stoffer S.S., McKeel D.W., Randall R.V., Laws E.R. Pituitary prolactin cell hyperplasia with autono-mous prolactin secretion and primary hypothy-roidism. Fertil Steril. 1981;36(5):682-5.
8. Wakim A.N., Polizotto S.L., Burholt D.R. Influence of thyroxine on human granulosa cell steroidogenesis in vitro. J Assist Reprod Genet. 1995;12(4): 274-7.
9. Givens J.R., Kohler P.O., John Wiley & Sons. Ovarian Disorders. Clinical Endocrinology, 1986 New York, 303 – 312.
10. Kumkum A., Kaur J., Gupta S., Narang P. A. Hyperprolactinemia and its correlation with hypothyroidism in infertile woman. Obstetrics and Gynecology of India. 2005; 56: 68-71.
11. Affia T., Ismat F., Adeela A., Nasir M., Muhammad K. A. The incidence of hyperprolactinaemia and associated hypothyroidism: local experience from Lahore PJNM. 2011;1:49-55.
12. Casulari L., Celotti F., Naves L., Domigues L., Papadia C., Persistance of Hyperprolactinemia After Treatment of Primary Hypothyroidism and withdrawal of Long Term Use of Estrogen. Arg Bras Endocrinol Metab. 2005; 49 :468-472.
13. K. Mohan and Mazher Sultana Follicle Stimulating Hormone, Luteinizing Hormone and Prolactin Levels in Infertile Women in North Chennai, Tamil Nadu J. B io s c i. Re s ., 2010; 1(4):279-284.
14. Azima Kalsum, Samina Jalali. Role of hyperprolactinemia in fertility. Pakistan Journal of Medical Research 2002; 41; 3-15.
15. Yamaguchi M., Aono T., Koike K., Nishikawa Y., Ikegami H., Miyake A. and Tanizawa O. Effect of nocturnal hyperprolactinemia on ovarian luteal function and galactorrhea. Eur. J. Obstet. Gynecol. Rep. Bio, 1991; 39:187-191.
16. Mc Neilly A. S. Prolactin and the control of gonadotrophin secretion. J. Endocrinol, 1987; 115: 1-5.