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ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2019, 8(1): 109-114

Status of Prolactin and Thyroid Hormone Level among Primary Infertility Patients Visiting Tertiary Care Hospital, Nepal

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ABSTRACT

Background: *Infertility is defined as the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. Hyperprolactinemia and thyroid dysfunction are associated with reproductive dysfunction and infertility. Hypothyroidism and hyperprolactinemia are found to be closely interrelated. This study aimed to observe the level of serum prolactin, free Tri-iodothyronine (fT3), free Thyroxine (fT4) and Thyroid stimulating hormone (TSH) in women with primary infertility and to correlate the level of serum prolactin with TSH.*
Methods: *This study was conducted on patients visiting infertility OPD at the Institute of Medicine (IOM), Nepal from February 2016 to January 2017. Total 50 women with primary infertility were included in this study and 50 age-matched healthy controls were taken. Serum levels of prolactin, fT3, fT4, and TSH were measured in all subjects.*
Results: *The mean age of participants was 26.8 years. The median serum prolactin (21.8) and TSH levels (4.5) were found to be significantly high in the case group ($p<0.001$). Out of the total subjects with hyperprolactinemia, 51.1% were found to have hypothyroidism. There was a moderately strong, positive and significant correlation between serum prolactin and TSH levels ($r=0.62$, $p<0.05$). ROC curve analysis showed that at a cutoff value of 22.5 ng/mL for serum prolactin, a sensitivity of 86% and specificity of 82% could be achieved for detecting hypothyroidism.*
Conclusion: *The high prevalence of hyperprolactinemia and thyroid disorders in primary infertility stresses the fact that all women coming for consultation due to infertility should be recommended to undergo thyroid function tests and prolactin estimation at early stages of infertility checkup.*

Keywords: Infertility, Hyperprolactinemia, Hypothyroidism

INTRODUCTION

According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), infertility 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 [1]. The term primary infertility is used for a couple who have never achieved a pregnancy despite cohabitation and regular sexual intercourse and secondary infertility 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 infertility during their reproductive lives [2]. This has led the problem of infertility to be recognized as a public health issue [3]. The cause of infertility lies within the female in 45% of the couples, male factor infertility in 30% and in the remaining 25% the cause is unexplained [4].

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 [5,6]. Excessive prolactin secretion causes reproductive dysfunction and infertility by decreasing the pulsatile release of Gonadotropin releasing hormone (GnRH) impairing pituitary production of Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) along with other disorders like amenorrhea and galactorrhoea [7,8].

Thyroid dysfunction reduces the chances of pregnancy and also adversely affects pregnancy outcome [9].

Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and infertility [10]. Hypothyroidism and hyperprolactinemia are found to be closely interrelated [11]. As hypothalamic thyrotropin releasing hormone (TRH) increases the secretion of both TSH and prolactin, serum prolactin levels may be increased in cases of hypothyroidism [12]. This study intends to assess the status of prolactin and thyroid hormone levels in patients of primary infertility.

PATIENTS AND METHODS

This was a hospital based, single center, cross-sectional study conducted in patients visiting the Infertility clinic of IOM, Tribhuvan University Teaching hospital (TUTH), Nepal from February 2016 to January 2017. A total of 50 women between 20-35 years of age with primary infertility were included in this study and 50 age-matched healthy women with proven fertility were taken as controls. The exclusion criteria adopted during case selection were infertility due to male factor, anatomical abnormalities of the urogenital tract interfering with fertilization and implantation and on treatment for thyroid disorders and hyperprolactinemia.

This study was approved by the Institutional Review Board, IOM, TUTH (Ref no. 200(6-11-E)/072/073). Informed consent was obtained from all participants and relevant history was recorded. Random blood samples were collected and centrifuged at 4000 rpm for 5 minutes and investigations were carried out on the same day of sample collection. Serum prolactin, fT3, fT4, and TSH were estimated using the fully automated Enhanced Chemiluminiscent Immunoanalyzer (ECi). Laboratory standard operating procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot, for the validation of the results.

The data was analyzed in the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois, USA version 20). Independent T-test and Mann-Whitney U test was applied for comparison of mean and median to see the difference between case and the control group at 95% confidence interval (CI) where p was considered to be significant at <0.05. To see the association between two quantitative variables Spearman's correlation was used considering the data was non-parametric and significance was considered for a p-value<0.05.

RESULTS

Out of 100 subjects selected, 50 were cases with age 27.2 ± 3.89 years and 50 were age matched controls with age 26.56 ± 2.75 years ($p>0.05$). The maximum percentage of subjects; 50% in the case and 54% in the control group was found between ages 26-30 years. Most of the subjects in both groups were euthyroid (54% in cases and 88% in controls). Subclinical hypothyroidism was seen in 36% of cases and 12% of controls. Only 2% had hyperthyroid in the case group. Among the cases, 68% and among the control group 22% women had increased prolactin level (Tables 1 and 2).

Table 1 Thyroid hormone status among the case and control group

Parameters	Case (n=50)	Control (n=50)	Total (n=100)
Euthyroid	27 (54%)	44 (88%)	71
Subclinical hypothyroid	18 (36%)	6 (12%)	24
Hypothyroid	4 (8%)	0 (0%)	4
Hyperthyroid	1 (2%)	0 (0%)	1
Total	50 (100%)	50 (100%)	100

Table 2 Distribution of prolactin in case and control group

Prolactin	Case (n=50)	Control (n=50)	Total (n=100)
Normal	16 (32%)	39 (78%)	55
High	34 (68%)	11 (22%)	45
Total	50 (100%)	50 (100%)	100

The mean serum value of fT4 was lower in cases as compared to controls (13.94 ± 4.95 in cases and 16.09 ± 3.22 in controls, $p<0.05$), even though both mean values were within the normal range. The mean values of fT3, however, were not significantly different between cases and controls ($p=0.16$). The difference in median levels of TSH (4.5 in cases compared to 2.4 in controls) and prolactin (21.8 in cases compared to 11.2 in controls) was found to be statistically significant ($p<0.05$, Mann-Whitney U) (Table 3).

Table 3 Comparison of serum TSH and prolactin among case and control group

Hormone	Case		Control		p-value
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	
TSH (0.46-4.68 µIU/mL)	8.31 ± 17.84	4.5 (0.02-100)	2.67 ± 1.28	2.4 (1.2-5.9)	<0.001
Prolactin (3-18.6 ng/mL)	25.09 ± 14.86	21.8 (5.8-92.1)	13.09 ± 5.43	11.2 (5.9-23.9)	<0.001

Out of 100 participants, 45 had hyperprolactinemia, of which 23 had increased level of TSH showing the incidence of hypothyroidism in hyperprolactinemic women to be 51.1% (Table 2). The Spearman's correlation showed a moderately strong, positive and significant correlation between serum prolactin and TSH levels ($r=0.62$, $p<0.05$) among the cases.

ROC curve analysis showed that at a cutoff value of 22.5 ng/mL for serum prolactin, a sensitivity of 86% and specificity of 82% could be achieved for detecting hypothyroidism (AUC=0.856, C.I lower bound 0.74, upper bound 0.96) for cases (Figure 1).

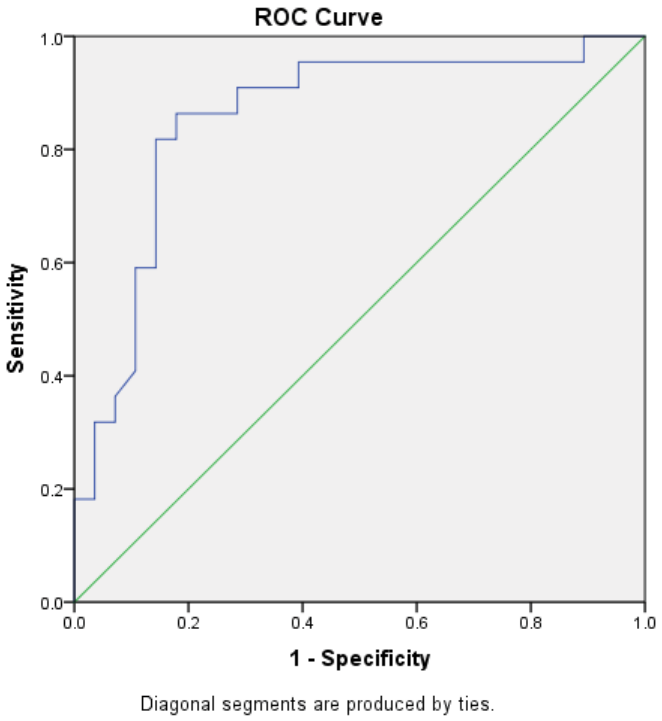

Figure 1 ROC curve for cases

DISCUSSION

The present study was conducted to measure the level of thyroid hormones and prolactin in patients suffering from primary infertility and to compare the results with that obtained from the subjects with proven fertility. Infertility represents a major life crisis to a large number of people, affecting them as individuals, as partners in marriage and as members of families and society [13].

Hyperprolactinemia is a common finding encountered in reproductive disorders and is a major cause of anovulation and female infertility [14]. As it has been understood that prolactin hypersecretion not only causes abnormalities like galactorrhoea and amenorrhoea but also leads to infertility, estimation of prolactin is being done in patients coming for consultation due to difficulty in conception. Fertility of an individual is also affected by the level of thyroid hormones. Thyroid dysfunction has been known to cause a broad range of reproductive disorders due to which evaluation of thyroid hormones is required for patients presenting with infertility.

In the present study, the level of serum prolactin was raised in 68% of the cases of infertility which was similar to

that reported by Prathibha, et al., (41%), Hymavathi, et al., (37%), Emokpae, et al., (33.7%) and Olooto, et al., (28%) [15-18]. The incidence of hyperprolactinemia in women with infertility was found to be somewhat lower in the studies conducted by Verma, et al., (18.27%) and Agrawal, et al., (11.5%) [19,20]. Stress, in part, is a contributing factor for hyperprolactinemia which can be attributed as one of the determining factors for the variable proportion of hyperprolactinemic patients in different studies [21].

The subjects in the control group had prolactin level in the range of 5.9 ng/ml to 23.9 ng/ml, with 22% having hyperprolactinemia. Stress during venipuncture can lead to a transient increase in the level of prolactin which can be the contributing factor of hyperprolactinemia seen in the control group [22]. Fewer than 10% of patients with idiopathic hyperprolactinemia ultimately are found to have a microadenoma [23]. In this study, among the hyperprolactinemic cases, none had value over 100 ng/mL. A pituitary adenoma is usually found to be the cause of hyperprolactinemia in cases with serum prolactin value more than 100 ng/mL [24]. As the level of prolactin in the hyperprolactinemic subjects in this study was less than 100 ng/mL, the possibility of the presence of adenoma is less.

Thyroid dysfunction interferes with female reproductive physiology due to which infertility may result. The ovaries are responsive to thyroid hormones due to the presence of thyroid hormone receptors in human oocytes [25]. Thyroid hormones also synergize with the FSH-mediated LH/human chorionic gonadotropin (hCG) receptor to exert direct stimulatory effects on granulosa cell function (progesterone production), and in *in vitro* studies, effects on differentiation of the trophoblast have been shown [26]. Another pathway through which hypothyroidism may impact on fertility is by altering the peripheral metabolism of oestrogen and by decreasing Sex Hormone Binding Globulin (SHBG) production [27].

Majority of the thyroid dysfunction in this study population was subclinical hypothyroidism (24%). The prevalence of subclinical hypothyroidism in women suffering from infertility has been reported to vary from 0.7% (Shalev, et al.,) to 43% (Gerhard, et al.,) [26]. Nepal is a country lying in the iodine deficient range with the overall prevalence of iodine deficiency as high as 13.52% [28]. The high prevalence of thyroid disorder found in this study may be due to the higher prevalence of iodine deficiency in this country.

The incidence of hypothyroidism in hyperprolactinemic women in this study was 51.1%. In the hypothyroid state, there is a compensatory increase in the discharge of TRH, potent prolactin releasing factor, thus resulting in increased prolactin secretion. There is also lack of negative feedback due to low serum levels of thyroid hormones which can cause proliferation and hypertrophy of both thyrotrophs and lactotrophs of the pituitary leading to the increase in the level of both TSH and prolactin [29]. Other mechanisms for this increase in prolactin may reduce secretion of some prolactin inhibitory factors, enhanced pituitary sensitivity to tonic TRH secretion, hyperplasia of TSH and prolactin producing cells [30].

Finally, the ROC curve analysis comparing TSH and prolactin levels using data from this study showed that there is a higher chance of thyroid dysfunction (notably hypothyroidism) co-existing with hyperprolactinemia at prolactin level above 22.5 ng/ml. One of the drawbacks of this study was that it only shows the measure of association between primary infertility and thyroid disorders and hyperprolactinemia. In order to establish the causation, further studies with large sample size are needed. The sample size in this study is small but in lieu of the exclusion criteria set which excludes all other causes of infertility like male factor and anatomical abnormalities of the urogenital tract interfering with fertilization and implantation, the subjects were mostly representatives of the women suffering from infertility due to hormonal causes which gave more reliable results on infertility due to hormonal causes.

CONCLUSION

Among the women having primary infertility, 2/3rd has increased the level of prolactin and almost half of them have thyroid dysfunction. About half of all the subjects having hyperprolactinemia have increased the level of TSH. From the ROC curve analysis, it can be deduced that a higher chance of having thyroid dysfunction coexists with hyperprolactinemia.

The high prevalence of hyperprolactinemia and thyroid disorders in cases of primary infertility stresses the fact that all the women coming for infertility checkup should be recommended to undergo thyroid function tests and serum prolactin estimation. This should be done as an initial line of infertility checkup rather than going for more costly and invasive procedures directly. The results further stress that serum TSH should be estimated in cases with

raised prolactin level to find the cases of hypothyroidism as the prevalence of hypothyroidism is more in cases of hyperprolactinemia.

DECLARATIONS

Acknowledgement

I would like to thank Dr. Rabin Gautam and Dr. Aseem Bhattarai for their continuous support and valuable contributions for this study.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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