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Thyroid Disorders and Prolactin Hormone and Their Association with Obesity in Infertile Women in a Tertiary Hospital of Nepal

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ABSTRACT

Introduction

Thyroid dysfunction has profound effects on menstrual function and female fertility. Hypothyroidism is often associated with increased prolactin level which again worsens the problem. This study was done to evaluate the prevalence of thyroid disorders in infertile women attending infertility outpatient department (OPD) in Tribhuvan University Teaching Hospital (TUTH) and to determine the association of hypothyroidism and hyperprolactenemia with obesity which is not well studied in our population.

Methods

A hospital-based cross-sectional study was conducted in infertility OPD of TUTH reviewing women's records who underwent infertility workup and relevant history, clinical finding and results of investigations including thyroid function test (TFT) and serum prolactin (PRL) level were documented. Descriptive and inferential statistical analyses were used to identify the prevalence and associations of predictors and outcome variables.

Results

Out of 213 participants, the majority of the participants were obese (90; 42.3%) with mean (±SD) body mass index (BMI) being 24.8 ± 4.5 kg/m^2. The prevalence of thyroid disorder was 18.4% including hypothyroidism 13.6% and hyperthyroidism 4.8%. There was no significant association of BMI and hyperprolactinemia with thyroid disorder as well as of BMI with hyperprolactinemia however the thyroid stimulating hormone (TSH) had significant positive correlation with prolactin ($r=0.23$, $p<0.001$).

Conclusion

Thyroid disorders and hyperprolactinemia are commonly observed in infertile women, so they should be routinely screened during initial evaluation of infertility. As majority of the study population were obese, despite no significant association of BMI with thyroid disorder and hyperprolactinemia, the effect of weight gain on infertility cannot be overlooked.

Keywords

Hyperprolactenemia, infertility, obesity, thyroid disorders

INTRODUCTION

Infertility is defined as the inability to conceive after 12 months of regular, unprotected intercourse.[1] The overall prevalence of infertility is estimated to range from 8-12%.[2] Female causes of infertility comprise endometriosis, tubal occlusion, and ovulatory dysfunction.[3-5] Thyroid dysfunction has a significant effect on menstrual function and female fertility.[3,6] It can cause anovulatory cycles, luteal phase defect, high serum prolactin (PRL) levels, and sex hormone imbalances leading to infertility.[4-10] Therefore, normal thyroid function is necessary for optimal fertility in order to achieve and sustain a healthy pregnancy. Elevated thyrotropin releasing hormone (TRH) levels in hypothyroidism are often associated with increased PRL levels.[6,7,9] Hyperprolactinemia also adversely affects the fertility potential by impairing pulsatile secretion of gonadotrophin releasing hormone (GnRH) and hence interfering with ovulation.[6,11] Because of their effect in infertility measurement of prolactin and thyroid hormones has been considered important component of infertility workup in women.

The association between obesity and hypothyroidism is well known.[12] However recent study has also shown that prolactin may be secreted from adipose tissue thus providing a link between obesity and hyperprolactinemia.[11] Thus this study aims to determine the interrelation of hyperprolactinemia and obesity with thyroid disorders and obesity with hyperprolactenemia, which is not well studied in our population, in addition to the determination of the prevalence and types of thyroid disorders in infertile women.

METHODS

This study is a hospital-based cross-sectional study conducted between March 2019 and March 2020 at infertility OPD of Tribhuvan University Teaching Hospital (TUTH). Women with primary and secondary infertility meeting inclusion criteria attending infertility outpatient department (OPD) were included in the study. Infertility was considered as primary if the couples are unable conceive for the first time while secondary if they are unable to conceive after an earlier pregnancy.[2] Women with history of thyroid disease, thyroid surgery or under thyroid medication, history of hyperprolactinemia or pituitary gland surgery or under medication for hyperprolactinemia were excluded from the study. Records having incomplete clinical information, reports of thyroid function test (TFT) or prolactin were also excluded from the study.

The sample size of 213 was calculated with 95% confidence interval taking 5% allowable error and 10% nonresponse rate, considering 7.7% prevalence of thyroid disorder among infertile women determined in previous study at same institute.[8] Women's records obtained from infertility OPD were reviewed. Detail clinical information such as age, menstrual cycles, type and duration of subfertility, history of thyroid disease, hyperprolactinemia or any medication use were noted. Anthropometric measurements of weight, height and body mass index (BMI) were noted. Quantitative determination of serum free T_3 (FT_3), free T_4 (FT_4), TSH and PRL in morning samples was done and the values of serum FT_3, FT_4, TSH level and serum PRL levels were also noted. The reference range of our laboratory was taken which are FT_3: 4.26- 8.1 pmol/L, FT_4: 10.2 -28.2 pmol/L, TSH: 0.46 – 4.68 µIU/ml and Prolactin in non-pregnant females: 2 to 29 ng/mL. The women were divided according to thyroid levels.

- Subclinical hypothyroidism: Raised TSH level >4.68mIU/ml and normal FT_4/FT_3 level.
- Overt hypothyroidism: Raised TSH level >4.68mIU/ml and low FT_4/FT_3 level.
- Subclinical hyperthyroidism: Low TSH level <0.46mIU/ml and normal FT_4/FT_3 level.
- Overt hyperthyroidism: Low TSH level <0.46mIU/ml and high FT_4/FT_3 level.

The diagnosis of hyperprolactinemia is made by a serum prolactin level above the normal range >30 ng/mL.

Obesity, determined by BMI, was calculated by weight in kilogram/(height in meter)^2 and classified according to ICMR Guidelines (2008) as follows[13]:

- Normal - 18 - 22.9 kg/m^2
- Overweight - 23 - 25 kg/m^2
- Obese - > 25 kg/m^2

The collected data were entered into Microsoft excel spread sheet and transferred into SPSS version 20.0 for statistical analysis. The descriptive results were presented in the form of mean, standard deviation, frequency and percentage for normally distributed data and non-normally distributed data were expressed as median and interquartile range. Fisher exact test was applied for categorical variables and independent sample t-test were performed for parametric test. The statistical significance was considered at p-value <0.05 and 95% confidence interval (CI). Ethical approval from the Institutional Review Committee of IOM and Research Department was taken before starting study (IRC reference number: 11(6-11) E^2 77/78).

RESULTS

Out of 213 participants, the majority of the study population had primary infertility (154; 72.3%) then secondary infertility (27.7%). Approximately two third (66%) of the participants were between 20 to 29 years age. In terms of BMI, majority of the

Table 1. Baseline characteristics of the study participants (n=213)

Variables	Mean/Frequency
Age (years)	27.7±4.2
Duration of infertility	2.9±2.7
Type of infertility	
Primary	154 (72.3%)
Secondary	59 (27.7%)
Menstruation irregularity	
Present	78 (36.6%)
Absent	135 (63.4%)
BMI (kg/m^2)	24.8±4.5
BMI category	
Underweight	8 (3.7%)
Normal	76 (35.7%)
Overweight	39 (18.3%)
Obese	90 (42.3%)
Hormone levels	
FT_3 (pmol/L)	5.5±1.2
FT_4 (pmol/L)	13.7±3.9
TSH (µIU/ml)	3.2±3.1
Prolactin (ng/mL)	19.7±11.1

Table 2. Distribution of thyroid and prolactin hormone disorders (n=213)

Hormone status	Frequency
Thyroid hormone	
Euthyroid	174 (81.6%)
Subclinical hypothyroidism	22 (10.3%)
Overt hypothyroidism	7 (3.3%)
Subclinical hyperthyroidism	5 (2.4%)
Overt hyperthyroidism	5 (2.4%)
Prolactin hormone	
Hyperprolactinemia	32 (15%)

Table 4. Association of BMI with Prolactin (n=213)

BMI Category	Normal prolactin	Hyper prolactinemia	p-value*
Underweight	7 (3.8)	1 (3.3)	0.53
Normal	61 (33.7)	15 (46.8)	
Overweight	35 (19.4)	4 (12.5)	
Obesity	78 (43.1)	12 (37.5)	

** Fisher's exact test*

participants were obese (90; 42.3%), followed by normal (35.7%) and overweight (18.3%) (Table 1).

In this study, the prevalence of thyroid disorder was 18.4% (39/213) including hypothyroidism 13.6% (29/213) and hyperthyroidism 4.8% (10/213). Subclinical hypothyroidism was the most common disorder comprising 10.3% (22/213) of cases (Table2). The prevalence of hyperprolactinemia was 15% (32/213).

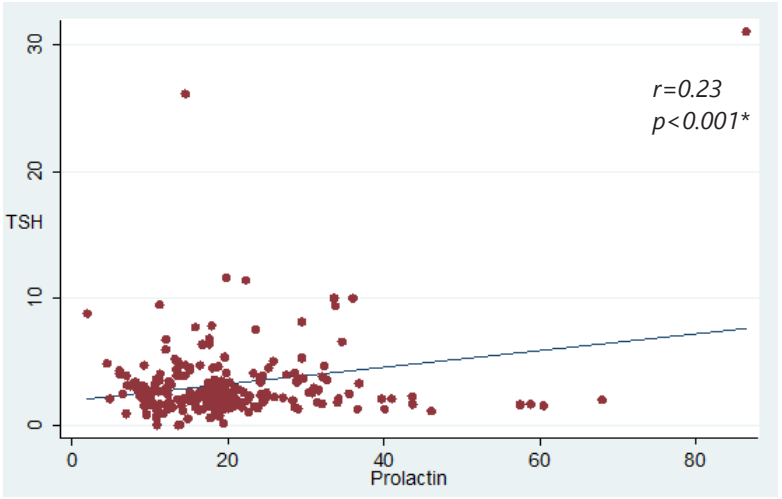
The mean (±SD) age of the participants was 27.7±4.2 years with range from 20 to 39 years (Table 1). While comparing the mean distribution according to type of infertility the mean age was significantly higher in secondary infertility (28.83±4.11) compared to primary infertility (27.35±4.17). The mean (±SD) BMI was 24.8±4.5 kg/m2 and it was in the obese range in the secondary infertility group, however the difference in BMI between the two groups was insignificant. The mean prolactin level was significantly higher in primary infertility than secondary infertility.

Table 3 depicts the association of BMI and hyperprolactinemia with thyroid disorder. In the current study, hypothyroidism was most prevalent in obese women (37.9%) and hyperthyroidism was more prevalent among those women who had normal BMI (60%). Similarly while evaluating association of BMI with hyperprolactenimia there

Table 3. Association of BMI, hyperprolactenimia, and menstruation irregularity with thyroid disorder (n=213)

Variables	Euthyroid n=174 (81.6%)	Hypothyroidism n =29 (13.6%)	Hyperthyroidism n=10 (4.8%)	p-value*
BMI				
Underweight	8 (4.6)	-	-	0.24
Normal	58 (33.3)	12 (41.3)	6 (60)	
Overweight	30 (17.2)	6 (20.6)	3 (30)	
Obesity	78 (44.8)	11 (37.9)	1 (10)	
Prolactin				
Normal	149 (85.6)	22 (75.8)	10 (100)	0.18
Hyperprolactinemia	25 (14.3)	7 (24.1)	0	
Menstruation irregularity				
Yes	65 (37.3)	9 (31)	4 (40)	0.80
No	109 (62.6)	20 (68.9)	6 (60)	

** Fisher's exact test*



* Pearson correlation

Fig 1. Correlation of prolactin with TSH level

was no significant association between the two (Table 4).The TSH has significant positive correlation with prolactin (r=0.23, p<0.001) (Fig 1).

DISCUSSION

In the present study the mean (±SD) age of the participants was 27.7 (±4.2) years which was similar to other studies.[3,8,10] The mean age was significantly high in secondary infertility compared to primary infertility which can be expected due to its selection criteria and was comparable with other study.[11] Among the study population majority were having primary infertility (72.3%) than secondary infertility (27.7%), finding in common with other studies.[3,7] Both hyperthyroidism and hypothyroidism may result in menstrual disturbances and in the present study 31% of hypothyroid women and 40% of hyperthyroid women had menstrual irregularity though the association was not significant.

Obesity by affecting hypothalamo–pituitary–gonadal axis can produce menstrual disturbances and subfertility.[11] Even after fertility treatment overweight and obese women have been shown to have poorer outcomes.[11] Hence weight loss should be advised to infertile women, if overweight or obese, along with the definitive treatment which will improve their hormonal imbalance thus favoring the treatment outcome. Proportions of high BMI in infertile women was obvious in this study as 60.6% of the study population were either overweight (18.3%) or obese (42.3%) and mean BMI was also in overweight range (24.8 ± 4.5 kg/m^2). The higher BMI in the secondary infertility group could be due to weight gain in previous pregnancy or due to older age, which is a common observation in another study.[11]

The prevalence of thyroid disorder among infertile women varies from 4.6% to 25.6% in different studies and in the current study it was 18.4%.[3,4,8,10] Hypothyroidism was the most common thyroid disorder (13.6%) the prevalence of which was similar to study conducted by sharma et al (17%).[14] However other studies have showed higher[6,7,9,10] as well as low prevalence3. Subclinical hypothyroidism was more common than overt hypothyroidism which is consistent with other studies.[6,7,9] Hypothyrodism is usually associated with weight gain and obesity with few studies showing significant association.[12] In the current study, hypothyroidism was most prevalent in obese women (37.9%) and 58.5% subjects with hypothyroidism were overweight or obese which was comparable to another study where 52.9% were overweight or obese.[14] Hyperthyroidism was observed in 4.8% in this study however lower (1%) and higher (5.4%) prevalence were reported in other studies.[10,14]

Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation.[11] In the present study the prevalence of hyperprolactinemia was 15% however other studies reported higher prevalence of 18.3%, 24.67%, 41% and 46%.[7,9,14,15] Consistent to other studies, hyperprolactinemia was seen more in primary than secondary infertility in the present study.[14,15,16] The mean prolactin level was significantly higher in primary infertility than secondary infertility which was also observed by Sharma et al.[14] However unlike this study there was no significant difference in a study done by Sheth et al.[11]

Hypothyroidism along with raised TSH level leads to rise in prolactin level resulting into hyperprolactinemia. Hence prolactin has been shown to correlate positively with TSH and to increase in proportion to increases in TSH levels.[4] Similar finding of significant positive correlation of the TSH with prolactin was determined in this study too. When the association of hyperprolactinemia

and hypothyroidism was evaluated, 24.1% (7 out of 22 patients) of hypothyroid women were found to have hyperprolactinemia, similar to another study.[9] Raised prolactin in hypothyroid women further worsen the condition interfering with treatment effectiveness. Thus in hypothyroid infertile women along with hyperprolactinemia treatment should be directed first to correct hypothyroidism before evaluating further causes of raised PRL levels as adequate thyroid supplementation restores PRL levels and normalizes ovulatory function.[10]

Recent study pointed out that prolactin may be secreted from adipose tissue as this study demonstrated significant positive correlation of body weight and BMI with serum prolactin in secondary infertility, thus providing a link between obesity and hyperprolactinemia.[11] However in the present study no significant correlation was noted between BMI and hyperprolactinemia though around 50% of women with hyperprolactenemia were either overweight or obese, finding comparable to another study (43.9%).[14]

CONCLUSION

Endocrinological disorders like thyroid disorder and hyperprolactinemia are commonly observed in infertile women. As they are associated with menstrual irregularities and infertility, routine screening for thyroid status is mandatory, along with PRL level, during initial evaluation of infertility. Though there was no significant association of BMI with thyroid disorder and hyperprolactinemia. The majority of the study population were obese that signifies that the effect of weight gain on infertility cannot be overlooked.

CONFLICT OF INTEREST

None declared.

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