Correlation of thyroid dysfunction with infertility in North Indian population

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ABSTRACT

Objective: The present study is to determine association of thyroid dysfunction along with clinical variables with infertility in North Indian population.

Materials and methods: The study was conducted in the department of Biochemistry with the collaboration of Department of Gynaecology RAMA MEDICAL COLLEGE, Kanpur. The study included 150 patients of infertile women in the age group of 20 to 40 years and 150 age and sex matched controls. Fasting venous blood samples were analysed for fasting thyroid profile. Mean difference between two continuous variables were tested using student sample t test. For testing the differences between the categorical variables, chi square test was used.

Results: The TSH level was significantly higher in the subjects with the infertility 6.57±4.9 and 5.31±4.8 in controls (P = 0.026). However, no significant difference was noted in the T3 and T4 level in cases as compared to controls.

Conclusion: The present study observed that hypothyroidism is a significant risk factor for infertility in North Indian population and prospective study with adequate power is required to validate the findings observed in the present study.

Keywords: Thyroid profile, infertility, North Indian population.

Introduction

Reproduction is the gift of God to all living creations and God has created this world for all his living creation to reproduce and flourish. In the Indian tradition fertility is considered as most imperative part of marital life. According to the Longman Dictionary of the Contemporary English, denotes to the “state of being fertile that is being able to produce many young, fruits or seeds.” for the definition of fertility. In Indian culture, as per the Indus Valley were believed to have worshipped the Mother Goddess, who was a symbol of fertility. Fertility is considered as vital factor in a woman’s life.

Infertility is defined as the failure of a couple to conceive after completing one year of regularly timed (at least three times per week) unprotected intercourse without conception (1), as well as being unable to carry a pregnancy to full term (2). Both male and female contribute for this condition. Primary infertility is that where a woman has not
Conceived even once in her life time. Secondary infertility is defined as inability to become pregnant or conceived after previously giving birth to a baby.

Infertility has been recognised as major public health issue due to its rising prevalence and incidence. During the past century, a worldwide increase in economic and social development agree with a widespread deterioration in human fertility has been observed (3).

Infertility has emerged as a significant common social condition and health care problem globally. Its prevalence varies from 9 to 18 percent in the general population in the reproductive age. It is estimated that 48.5 million to 186 million women experience infertility in their reproductive age (4).

India is facing significant challenge due to infertility with its prevalence in India varies between 3.9 to 16.8% in different states of India. Its estimates greatly varies in different states of India from 3.7 % in Uttar Pradesh, Himachal Pradesh and Maharashtra, (5) to 5% in the Andhra Pradesh, (6) and 15% in Kashmir(7). The inability to have children has great impact on the social, psychological and emotional distress in society especially in couples.

Despite its various social implications, the care and prevention of the infertility remains highly neglected especially in the low- and middle-income countries.

Hypothyroidism has been observed as an important significant risk factor for infertility specially in low and middle income countries therefore, aim of the present study is to determine aassociation of thyroid dysfunction along with clinical variables with infertility in North Indian population.

MATERIAL AND METHODS

Study was conducted in the department of Biochemistry with the collaboration of Department of Gynaecology RAMA MEDICAL COLLEGE, Kanpur.

STUDY DESIGN: Hospital based Case Control study

ETHICAL CONSIDERATION

The study was approved by the Ethical Committee of Institution. A written informed consent, in the vernacular language was obtained from all the participants, upon fulfilling the inclusion criteria. Confidentially of each patient’s data was maintained.

METHOD OF SAMPLING AND DATA COLLECTION

The convenience method of sampling was used for the selection of subjects for the present study. Data was collected in the standardized data collection form.
Eligibility criteria

The study subjects were recruited into the study if they were fulfilling the following inclusion and exclusion criteria

INCLUSION CRITERIA

- Diagnosed case of infertility in the age group of 20 to 40 years attending the OPD of Obstetrics & Gynaecology Department of Rama Medical college and Hospital
- Able to provide the written informed consent form
- In good physical state
- Negative serum Hepatitis B, Hepatitis C virus (HCV) and HIV

EXCLUSION CRITERIA

- Female with any other reproductive disorder
- Husband have any reproductive disability
- Female below 20 and above 40-year group
- Known history or acquired thrombophilia
- Known Tumors in any part of body
- Known current active pelvic inflammatory disease

METHOD OF EXAMINATION

For each case overnight fasting 5ml venous blood sample was collected from antecubital vein under aseptic precaution then separated serum by centrifugation, within an hour and store it at -2 to -4 0°C until biochemical analysis.

BIOCHEMICAL PARAMETERS-

- Thyroid profile
  
  Method e-chemiluminous based method by cobas e 411 machine was used.
  
  Principal: Thyroid stimulating hormone is a glycoprotein which has the 3000 daltons molecular weight and possess two subunits. The beta-subunit carries the TSH-specific immunological and biological information whereas another unit which is called alpha subunit possess the species-specific evidence.
Normal range of thyroid hormone:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>T3</td>
<td>chemiluminous</td>
<td>1.32-3.1 nmol/l</td>
</tr>
<tr>
<td>T4</td>
<td>chemiluminous</td>
<td>66-181 nmol/l</td>
</tr>
<tr>
<td>TSH</td>
<td>chemiluminous</td>
<td>0.27-4.20 microlU/ml</td>
</tr>
</tbody>
</table>

**Statistical analysis**

Descriptive statistical were used to describe the baseline and demographics data. Continuous variables were represented using mean and standard deviation and categorical variables were represented as number and percentages. Mean difference between two continuous variables were tested using student sample t test. For testing the differences between the categorical variables chi square test was used. Logistic regression analysis was done to find out the predictor for the outcome variables and multivariable logistic regression analysis was used for the adjustment of confounder and to determine the independent effect of risk factor variables. P value and less than 0.05 was considered statistical significant level.

**Sample size**

Sample size has been calculated in order to control type I & type II error. Assuming a minimum power 80% and 95% significance level the sample size has been calculated using this formula.

Following the literature, the incidence of infertility has been assumed between 5 to 10%. Keeping this value with 80% power and 5% alpha we estimate the sample size of 135 each group. In order to control loss of follow up and manual errors, we rounded the sample size of 150 for each group total (300).

**Results**

A total of 300 subjects (150 cases and 150 controls) were recruited from the Obstetrics and Gynaecology Department, RAMA Medical College undergoing the treatment for infertility. Mean age of cases was 29.64±4.1 and in controls subjects was 29.9±5.21. The both the groups were balanced as observed by the insignificant p value using parametric independent sample student t test (P = 0.63). In the case subjects a total of 115 were belonged to Hindu religion and 35 from Muslim religion, while in the control subjects a total of 118 were from the Hindu religion and 32 from Muslim community. Duration of marriage was varied from 1 to 22 years with the mean 7.4±4.8 years. The mean age of the duration of marriage in cases was 5.81±3.3 years while in the controls was 9.1±5.4 years and statistically significant (P<0.001). In the infertile women the mean age at the time of diagnosis was 27.4±3.37. A total of 129 women were diagnosed with the primary infertility and 21 were with secondary infertility. There was significantly low number of
infertilities in the low economic status compared to control and this difference was statistically significant (P< 0.001). Chi square for trend suggested significant trend in association of economic status in infertility when compared with controls (P trend<0.001). The more subjects with infertility resided in Urban area as compared to Normal fertile women (P <0.001). Subjects with infertility were more educated as compared to controls. The sedentary occupation was also significantly associated with risk of infertility as shown in Mean of BMI was also higher in the cases as compared to controls which was noted in the independent sample t-test (Table and figure). The TSH level was significantly higher in the subjects with the infertility 6.57±4.9 and 5.31±4.8 in controls (P = 0.026) (Table 1 and Figure 1), however no significant difference was noted in the T3 (Table 2 and Figure 2) and T4 level in cases as compared to controls (Table 3 and figure 3).

Discussion

In the present study the association between the important risk factors (stress, obesity, thyroidism) and infertility was studied using the case control study in North Indian population. Overt hyperthyroidism may induce the imbalance in the estradiol metabolism and escalation of gonadotropin in response to sex hormone like gonadotroin-releasing hormone. In view of this the baseline gonadotropin concentrations are also found to be increased. A study showed that there is dramatic reduction in the irregular menstrual cycle in case of early detection and treatment of hyperthyroidism (13). The occurrence of primary and secondary infertility associated with the hyperthoroidism has been reported to be 0.9 to 5.8% (14).

A study by Rao M in 2019 (15), conducted a systematic review and meta-analysis on topic “Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity including 13 studies involving 7970 concluded that LT4 supplementation is associated with significant decrease in pregnancy loss (RR 0.56, 95% CI 0.42 to 0.75) and also with the preterm birth rate (RR=0.68, 95% CI 0.51 to 0.91). Another meta-analysis by Rao M 2018 (16) included four randomized controlled trials to check whether levothyroxine supplementation would improve the pregnancy outcome in subject with infertility who underwent in vitro fertilization or intracytoplasmic sperm injection. This pooled analysis of this study noted that no significant association of LT4 treatment with the clinical pregnancy rate (Risk ratio = 1.46, 95% CI 0.86 to 2.48), live birth rate (Risk ratio = 2.05, 95% CI 0.96 to 4.36), or preterm birth rate (Risk ratio =1.13, 95% CI: 0.65 to 1.96), However, significant reduction in the miscarriage rate compared to placebo was noted in women receiving LT4 supplementation. The finding of this study concluded that given the potential to reduce miscarriage rate, LT4 supplementation is recommended for subjects with infertility having subclinical hypothyroidism. Korevaar TIM in 2018(17) published a study in Thyroid Journal with an aim to determine the relationship of thyroid function and autoimmunity markers with ovarian reserve day three FSH and antral follicle count (AFC) and to investigate whether the any association with thyroid autoimmunity with diminished AFC. This study included 436 women with 530 AFC measurement. Authors reported that lower fT3 and TPOAb positivity were associated with diminished antral follicle count (AFC) in female with unexplained infertility and concluded that future studies are required to corroborate these findings. A another systematic review and meta-analysis
by Li J 2017 et al (18) indicated that supplementation of LT4 is associated with increased in clinical pregnancy, and fertilization rates. This study concluded that beneficial effects in pregnancy outcomes among patients with thyroid dysfunction with the supplementation of LT4, thus it should be recommended to improve the clinical pregnancy in subjects with infertility and having thyroid dysfunction.

The findings of our study is consistent with the studies reported in the literature which showed that hypothyroidism is associated with the increased risk of infertility, poor ovarian reserve in women in reproductive age. (16). Several studies have shown the positive outcome after the Levothyroxine supplementation on assisted reproductive technology (19). The consistent high prevalence of thyroid disorders in polycystic ovarian subjects has been observed and pointed out the early correction of hypothyroidism in the management of infertility associated with PCOS.

**Conclusion**

The present study observed that hypothyroidism is a significant risk factor for infertility in North Indian population and prospective study with adequate power is required to validate the findings observed in the present study.

**References:**

4. WHO. Infecundity, infertility, and childlessness in developing countries. DHS Comparative Reports no. 3 Calverton, Maryland, USA: ORC Macro and the World Health Organization; 2004.


Table 1. Comparison of TSH level between cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Control</th>
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<tbody>
<tr>
<td>Mean</td>
<td>6.57</td>
<td>5.31</td>
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<td>Standard deviation</td>
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<td>4.80</td>
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<td>Standard error</td>
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<td>0.39</td>
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<tr>
<td>Total Number</td>
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<td>150</td>
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<tr>
<td>t- value</td>
<td>2.23</td>
<td></td>
</tr>
<tr>
<td>Mean Difference</td>
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<td></td>
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<tr>
<td>P value</td>
<td>0.026</td>
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Table 2. Comparison of T3 level between cases and controls

<table>
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<td>Mean</td>
<td>1.51</td>
<td>1.44</td>
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<tr>
<td>Standard deviation</td>
<td>1.35</td>
<td>1.13</td>
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<tr>
<td>Standard error</td>
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<td>0.09</td>
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<td>t- value</td>
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<td>P value</td>
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Table 2. Comparison of T4 level between cases and controls

<table>
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<td>Mean</td>
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<tr>
<td>Standard deviation</td>
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<tr>
<td>Standard error</td>
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<td>0.27</td>
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<tr>
<td>Total Number</td>
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<td>150</td>
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<tr>
<td>t-value</td>
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<td>2.32</td>
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<td>P value</td>
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Figure 3