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THYROID DYSFUNCTION IN INFERTILE WOMEN

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ABSTRACT

Background: *Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function. Thyroid dysfunction has a great impact on fertility in women.* ***Aim:*** *To assess the thyroid status in primary infertile women.* ***Materials and Methods:*** *A total of 100 subjects comprising of 50 primary infertile women as cases and 50 age matched healthy euthyroid fertile women as controls were included in the study.* ***Results:*** *Mean serum T3 and T4 were significantly increased (p<0.01), while TSH levels were significantly decreased (p<0.01) in infertile women when compared to controls. 42% of the infertile women were having thyroid dysfunction, out of which 20% were subclinical hyperthyroidism, 6% overt hyperthyroidism, 12% subclinical hypothyroidism and 4% were overt hypothyroidism.* ***Conclusion:*** *The study indicates association of thyroid dysfunction in infertility. Subclinical thyroid dysfunction was dominant thyroid disease in infertile women. Thyroid profile should be kept in consideration during the diagnosis and management of infertility.*

KEYWORDS

Infertility, thyroid dysfunction, thyroid profile, subclinical hyperthyroidism, subclinical hypothyroidism.

INTRODUCTION

Infertility is the inability of a couple to conceive after one year of regular unprotected intercourse. Its prevalence is estimated to be 10-15% in any community[1]. It is therefore a common condition with important medical, economic and psychological implications. Thyroid hormones are essential for normal growth, sexual development and reproductive function. Both hypothyroidism and hyperthyroidism are associated with a variety of changes in reproductive functions including delayed onset of puberty, menstrual disorders, anovulatory cycles, infertility and reproductive wastage when pregnancy is achieved [2,3,4]. Thus thyroid dysfunctions may have a great impact on fertility in females[5]. Undiagnosed and untreated thyroid disease can be a cause for infertility as well as sub-fertility. The prevalence, screening and treatment of sub-clinical thyroid disorders in infertility patients have been discussed in many studies, but no consensus has been obtained [6].

Evaluation of thyroid status in the infertile couple is not only important because it is significant and most common but also its treatment is very simple and often has reversible or preventable effects on infertility [7, 8]. Data on relationship between subclinical thyroid dysfunction and infertility remain scarce as these subgroups of infertile patients passes unrecognized. Due to the lack of population-based infertility data of women with subclinical thyroid dysfunctions in our state, we planned to evaluate the thyroid status in infertile women.

MATERIALS AND METHODS

A case control study was conducted in Department of Biochemistry, JJMMC, for a period of one year. Fifty female patients between the age group of 20-35 years, who were being examined by

gynecologists and diagnosed as primary infertility, were included as cases in the study. Inclusion criteria were history of at least one year infertility with normal semen analysis of husband. They were compared with fifty age matched healthy euthyroid fertile women. The infertile women having tubular blockage, pelvic inflammatory disease, endometriosis, genital TB and with liver, renal or cardiac diseases; those already on treatment for thyroid disorders or cases where abnormality was found in husband's semen analysis were excluded from the study.

The study was approved by institutional ethical committee and was conducted after taking informed, written consent of the participants. After taking all the aseptic precautions, about 2 ml of venous blood was drawn in a plain bulb. The blood was allowed to clot and the serum was separated by centrifugation at 3000rpm for 15 minutes. The samples were refrigerated at 2-8^{o}C for maximum period of 5 days, if not tested immediately.

Thyroid status was evaluated by measuring serum T3, T4 and TSH by chemiluminiscence immunoassay method [9], using Acculite microwells on LUMAX 4101 (Monobind inc. USA). Before processing the samples, each method was calibrated.

Statistical Analysis

All the data analysis was performed using SPSS version 17.0 (SPSS inc, Chicago, IL USA). The values were expressed as Mean ± S.D. Students't' test was used and a p value of <0.05 was taken as statistically significant.

RESULTS

The present study includes 50 infertile women as cases and 50 age matched healthy fertile women as controls.

Most of the patients were in the age group of 24 – 28 years and the average duration of infertility was 5 years or less. As shown in **Table 1**, serum T3, T4 levels were found to be significantly increased in infertile females compared to controls ($p<0.01$). Serum TSH levels were found to be decreased in infertile females compared to the controls and it was also statistically significant ($p<0.01$).

Table 2 summarizes the percentage prevalence of thyroid dysfunction in primary infertile females. Out of 50 primary infertile patients enrolled in the study, 8(16 %) infertile women had increased TSH (>5.45µIU/ml) and 13(26 %) infertile women had decreased TSH levels (<0.28µIU/ml). Depending on the T3 and T4 levels, all the 21(42 %) thyroid dysfunction cases were further subdivided into overt or subclinical thyroid dysfunction, which showed 4 % overt hypothyroidism, 12 % subclinical hypothyroidism, 6 % overt hyperthyroidism while 20 % were of subclinical hyperthyroidism.

Table 1: Thyroid profile in case and control group

Parameter	Cases (infertile women) (n = 50)	Controls(fertile women)(n = 50)
T3(ng/ml)	1.5 ± 0.56 [a]	0.9 ± 0.35
T4(µg/dl)	9.8 ± 2.85 [a]	7.7 ± 1.97
TSH(µIU/ml)	1.4 ± 1.65 [a]	3.7 ± 1.03

All the values were expressed as Mean ± S.D,
n is number of cases /controls,
[a] p value <0.01 is statistically significant when compared to controls.

Table 2: Percentage prevalence of thyroid dysfunction in infertile group

Type of the cases	No. of cases	Percentage
Overt hypothyroidism	2	4.0
Subclinical hypothyroidism	6	12.0
Overt hyperthyroidism	3	6.0
Subclinical hyperthyroidism	10	20.0
Euthyroidism	29	58.0

DISCUSSION

Female infertility occurs in about 37% of all infertile couples and ovulatory disorders account for more than half of these[10]. Thyroid hormone have profound effects on reproduction and pregnancy. Both subclinical hyperthyroidism and subclinical hypothyroidism are increasingly being recognized as having significant health implications. In both the conditions, the serum concentration of circulating thyroid hormones, T3 and T4 are within the normal reference ranges. TSH levels are low or suppressed in subclinical hyperthyroidism and elevated in subclinical hypothyroidism [11]. Recent data indicate that variations of free T4 (fT4) in the individual are narrower than variations within the reference range for the population. These data may indicate that normal fT4 (for the population reference range) could reflect an abnormal fT4 for the individual patient with increased serum TSH [12].

In the present study, there is statistically significant increase in mean serum T3 and T4 and decrease in TSH levels in infertile women when compared to controls. Hyperthyroidism (26%) was more prevalent than hypothyroidism (16%) in our study. This is in accordance with the report of Singh et al [13]. The prevalence of thyroid dysfunction in infertile women was found to be 33.3% in a study by Rahman et al, [14] and 23% by Sharma et al. [15]. In our study, thyroid dysfunction was present in 42% of the infertile women. It is obvious from the observation that fertility of female reproductive system is hampered by altered thyroid hormone levels. Majority of the patients were in euthyroid state which may be due to other cause of infertility.

The prevalence of hypothyroidism in the reproductive age group and defined as a abnormally elevated TSH concentration, ranges from 2-4 % [16,17] which is found to be 6.7% by Rahman et al [14], 8% by Goswami et al [18] and 20 % by Sharma et al [15] while in our study this prevalence was 16%. Subclinical hypothyroidism is associated with ovulatory dysfunction[19]. Previous studies revealed variable data on prevalence of subclinical hypothyroidism in infertility, 25% by Bals Pratsch et al [20] and 4.6% by Grassi et al [21]. In our study, 12 % infertile women were suffering from subclinical hypothyroidism. Also subclinical hypothyroidism was more common than overt hypothyroidism in the present study, which is in accordance with Verma et al [22].

The impact of hypothyroidism on ovulation and menstrual function is related to numerous interactions of thyroid hormones with the female reproductive system, thus finally leading to infertility. In hypothyroidism, increased TRH production leads to hyperprolactinaemia and altered GnRH pulsatile secretion. This leads to a delay in LH response and inadequate corpus luteum leading to abnormal follicular development and ovulation. Thyroid hormones receptors are expressed in human oocytes and granulosa cells. At the cellular level, thyroid hormones synergize with the FSH-mediated LH/hCG receptor to exert direct stimulatory effects on granulosa cell function (e.g. progesterone production) [23]. Another pathway by which hypothyroidism may impact on fertility is by

altering the peripheral metabolism of estrogen and by decreasing SHBG production. Both pathways may result in an abnormal feedback at the pitutary level [24].

Disturbances in normal pulsatile release of LH and hyperprolactinaemia can result in menstrual dysfunction, ranging from anovulatory cycles with menorrhagia, oligomenorrhea or amenorrhea [23]. In a study on Indian women, Joshi et al found 68.2% of menstrual abnormalities in hypothyroid women compared with 12.2% of healthy controls [25].

The prevalence of hyperthyroidism was about 23% by Singh et al [13], 8% in the study by Goswami et al [18] and 5.8% by Joshi et al [25]. Relatively higher prevalence of Hyperthyroidism (26%) in our study could be due to special referral pattern of the patients from a specific area for thyroid profile.

The precise impact of hyperthyroidism on fertility remains ill-defined. In general prevalence of subclinical hyperthyroidism is 1.5% and menstrual abnormalities are 2.5 times higher than general population. Studies on the association between subclinical hyperthyroidism and infertility are scarce and often surrogate such as the menstrual pattern are investigated rather than specific endpoints such as pregnancy rates and/or outcome[26]. In contrast to the hypothyroidism, SHBG production is increased in hyperthyroidism. Therefore the metabolism of estrogen is altered and the conversion of androgens to estrogens is increased. Hyperthyroidism also increases the gonadotropin response to GnRH and the baseline gonadotropin concentrations are also frequently elevated. The decrease in menstrual flow may also relate to effects on haemostatic factors, including the synthesis of factor VIII [27].

Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones. The decision to initiate thyroid correction therapy in subclinical thyroid dysfunction at early stage is justified in infertile women. Our data also indicate that variations in TSH levels in the narrower range should not be ignored in infertile women who are otherwise asymptomatic for clinical hyperthyroidism. This group of infertile women, if only carefully diagnosed and treated for hyperthyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures. For better management of infertility case, we should plan further studies with the large sample size and investigate the beneficial effect of drug treatment by long-term follow-up, which are necessary to validate the variation in T3, T4 and TSH levels. In addition to thyroid profile other endocrine hormones like prolactin should be considered in infertility.

CONCLUSION

Our study reveals that subclinical thyroid dysfunction is more prevalent than overt thyroid dysfunction in infertile women. Hyperthyroidism seems to be dominant thyroid dysfunction in infertile women. These disorders may lead to menstrual irregularities and anovulation resulting in infertility. Hence, estimation of serum T3, T4 and TSH levels should be included in the infertility workup. The patient may be treated accordingly with medications and can revert back to the fertile state.

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