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Study of Thyroid Dysfunction in Association with Infertility

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Authors' contributions

This work was carried out in collaboration between both authors. Author AKS designed the study, wrote the protocol and supervised the work. Author PPH carried out all laboratories work, performed the statistical analysis and managed the analyses of the study. Author PPH wrote the first draft of the manuscript, managed the literature searches and edited the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the relation of female infertility to thyroid dysfunction.
Study Design: This is a descriptive, hospital-based study.
Place and Duration of Study: The present study was carried out in the department of Biochemistry in collaboration with the Gynae and Obst department, Ashwini Rural Medical College, Hospital and research centre Solapur. Over the period of 6 month from August 2015 to January 2016.
Methodology: The study group included 60 cases among which 48 women were having primary infertility & 12 women had secondary infertility, while control group included 40 fertile euthyroid women. Serum T3, T4 and TSH estimation was done by Enzyme linked fluorescent assay on mini VIDAS.
Results: In hyperthyroid FT3 level 21.33±7.31 pmol/L, in hypothyroid 3.52±1.20 pmol/L (P value < 0.001, i.e., highly significant), and in euthyroid 4.19±0.58 pmol/L (P value > 0.05, i.e., not

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significant), 4.17±0.80 pmol/L, when compared with control. FT_4 level was 52.7±4.52 pmol/L in hyperthyroid (p value <0.001. i.e. highly significant), while in hypothyroid 9.80±5.5 pmol/L, and in euthyroid 13.82±3.48 pmol/L (P value > 0.05, i.e. not significant), 14.63±2.85 pmol/L, when compared with control. Serum TSH level in hyperthyroid was 0.22±0.10 µIU/ml, in hypothyroid 21.98±19.86 µIU/ml (P value < 0.001, i.e. significant), 2.61±1.24 µIU/ml in euthyroid (P value > 0.05, i.e. not significant); 2.72±1.51 µIU/ml when compared with control.

Conclusion: Thyroid hormones play an important role in normal reproductive function, both through direct effects on the ovaries and also indirectly by multiple interactions with other sex hormones. Therefore, thyroid dysfunction can lead to menstrual irregularities and, thus, finally to infertility.

Keywords: Thyroid dysfunction; infertility; hypothyroidism; hyperthyroidism.

1. INTRODUCTION

Infertility is the failure of couple to conceive a pregnancy after trying to do so for at least one year. Infertility has increased as a problem over the last 30 year. Infertility although, is not lethal but the desire to reproduce is a basic human instinct & deprivation of fertility may lead to guilt & depression. Approximately one tenth of marriages are barren & 10% have fewer than desired number of children. If female fails to achieve pregnancy after one year of unprotected & regular sexual intercourse, it is an indication to investigate the couple. Although consative factor (33%), female is as fault in the predominant number of case. It should be remembered that infertility is not a disease & the couple generally is otherwise healthy, they should be encouraged to be active in their evolution & in determining their course of therapy [1-3].

Endocrine system is the second key regulator of organ system function after nervous system. Hormones are the messengers in endocrine signaling. Thyroid gland controlling brain & somatic development in infants & metabolic activities in adults upon stimulation by thyroid gland secretes thyroid hormones; triiodthyronine (T_3) & thyroxin (T_4). Thyroid hormones have a role in controlling basal metabolism rate, growth as well as the development & differentiation of many cells in the body [3,4].

Fertility in female is maintained by prevailing hormonal milieu, which is delicately balanced by hypothalamic pituitary thyroid adrenogonadal axis. Infertility is common accompaniment of disorders of thyroid function. Abnormalities of thyroid function hypo as well as hyperthyroidism are associated with variety of changes in reproductive system, including delayed onset of puberty, menstrual irregularities & recurrent fetal wastages. Anovulation is more commonly noted in association with hyperthyroidism. Significant interrelations have been found between thyroid disorders & gonadal functions by various laboratory & clinical studies [3,4]

Therefore the present study has aim to evaluate thyroid status in the infertile women. For this certain biochemical parameters were done. These included T3, T4 and TSH by using Enzyme Linked Fluorescent Assays technique.

2. MATERIALS AND METHODS

2.1 Study Design

This study was carried out on 100 women selected from outpatient & inpatient department of obstetrics and gynecology, Ashwini Rural Medical College, Hospital & Research center, Solapur, Maharashtra. Over the period of 6 month after taking consent from the subjects. Ethical clearance was obtained from the institution. The sample size calculate from hospital based gynae and obst department population. Women with diagnosed or medications likely to affect thyroid function were excluded.

The study has been carried out in biochemistry department for thyroid profile evaluation, study group included 60 cases among which 48 women were having primary infertility & 12 women had secondary infertility, while control group included 40 fertile euthyroid women.

2.2 Assay of Thyroid Function

Thyroid function test panel (T_3, T_4 and TSH) were assayed by Mini Vidas technique using standard kit.

T_3 and T_4 were assayed by competitive enzyme immunoassay method with final fluorescent detection (ELFA). The Solid Phase Receptacle (SPR) serves as solid phase as well as the pipetting device for the assay. Reagents for the assay are ready to use and pre dispensed in the sealed reagent strips.

All of the assay steps are performed automatically by the instruments. The reaction medium is cycled in and out of the SPR several times. The sample is collected & transferred into the well containing an Alkaline Phosphatase labeled anti T_3 & anti T_4 antibody (conjugate).

The antigen present in the sample and the T_3, T_4 antigen coated on the interior of the SPR compete for the available sites on the specific T_3, T_4 antibody conjugates to alkaline phosphatase.

During the final detection step, the substrate (4 methyl-umbelliferyl phosphate) is cycled in & out of the SPR. The conjugate enzymes catalyze the hydrolysis of this substrate into fluorescent product (4 methyl-umbelliferone). The fluorescence of which is measure of at 450 nm. The intensity of the fluorescence is inversely proportional to the concentration of antigen present in the sample. At the end of the assay result are automatically calculated by the instrument in relation to the calibration curve stored in memory, & then printed out.

The TSH was assayed by one-step enzyme immunoassay sandwich method with final fluorescent detection (ELFA). When the sample is transferred into the well containing anti TSH antibody labeled with alkaline phosphatase. The sample conjugate mixture is cycled in & out of SPR. The antigen binds to antibodies coated on SPR & conjugate forming a " sandwich " unbound component are eliminated during the washing steps, during the final detection step the substrate is cycled in & out by the SPR. the conjugate enzymes catalyzes the hydrolysis of this substrate into a fluorescent product which measure of 450 nm.

All the three parameters were estimated by following the same standard protocol provided by the manufacture (M/S Biomerieux) [5-7]. The normal ranges of FT3 is 2.15 to 8.65 pmol/L, FT4 is 9 to 22 pmol/L, and TSH is 0.25 to 5 µIU/ml for our laboratory. The cutoff level for hyperthyroidism is TSH > 0.25 µIU/ml and for hypothyroidism TSH < 5 µIU/ml.

2.3 Criteria of Thyroid Dysfunction

Thyroid function is considered normal (Euthyroid) when subjects were presented with normal T_3, T_4 & TSH. Abnormal thyroid function was further categorized as hyperthyroid (increased T_3, T_4 & decreased TSH), Hypothyroidism (decreased T_3, T_4 & increased TSH). In Subclinical hyperthyroid (normal T_3, T_4 & low TSH) & in subclinical hypothyroidism (normal T_3, T_4 & elevated TSH).

2.4 Statistical Analysis

Data were represented as percentage frequency, mean & standard deviation student "t" test and SPSS 17 software. The difference in mean values of various parameters was calculated and express in terms of P value.

3. RESULTS

The present study on "thyroid dysfunction in association with infertility", was conducted to correlate the role of T3, T4 and TSH as causative agent for infertility among females. The patients were divided as follows; study group included 60 patients of primary and secondary infertility. The control group contains 40 healthy fertile women of reproductive age group.

All the patients taken for study were in reproductive age group. Out of 60 patients in study group, 48 cases (80%) were having primary infertility and 12 cases (20%) secondary infertility [Table 1].

Out of 60 infertile women in study group, 21 (35%) cases of primary infertility and 2 (3.3%) cases of secondary infertility were of 20-25 years age; 20 (33.3%) patients of primary infertility and 3 (5%) patients of secondary infertility belonged to 26-30 years age, 5 (8.3%) patients of primary infertility and 5 (8.37%) cases of secondary infertility were between 31 and 35 years age and 2 (3.3%) in each group belonged to age more than 35 years age. So the maximum patients of primary were in age group 20-30 years while in secondary infertility 31-35 years age group. Among the 40 controls cases, 10 (25%) women were 20-25 years, 21 (52.4%) women of 26-30 years age, 8 (20%) belonged to 31-35 year age and only 1 (2.5%) cases above 35 year age [Table 1].

Among study group, 2(3.3%) hyperthyroid patients had serum FT3 level 21.33±7.31 pmol/L

(P value < 0.001 i.e., highly significant), in 24 (35.4%) hypothyroid patients 3.52±1.20 pmol/L (P value < 0.001, i.e., highly significant), and in 34 (56.6%) euthyroid women 4.19±0.58 pmol/L (P value > 0.05, i.e., not significant), when compared with control group of 40 women (100%) with serum T3 level 4.17±0.80 pmol/L [Table 2].

Serum FT_4 level was 52.7±4.52 pmol/L in 2(3.3%) hyperthyroid women (P value <0.001. i.e. highly significant), 9.80±5.5 pmol/L in 24 (40%) hypothyroid women (P value > 0.05, i.e. not significant), 13.82±3.48 pmol/L in 34 (56.6%) euthyroid group women (P value > 0.05, i.e. not significant), when compared with control group 60 (100%) women were in euthyroid range with serum T4 14.63±2.85 pmol/L [Table 2].

Serum TSH level in 2 (3.3%) hyperthyroid women was 0.22±0.10 µIU/ml (P value < 0.001, i.e. significant); 21.98±19.86 µIU/ml in 24 (40%) hypothyroid women (P value < 0.001, i.e. significant), 2.61±1.24 µIU/ml in 34 (56.6%) euthyroid group women (P value > 0.05, i.e. not significant; When compared with control group 60(100%) women who had serum TSH levels 2.72±1.51 µIU/ml. [Table 2]

Out of 48 patients of primary infertility, 2 (3.3%) were hyperthyroid, 19 (26.2%) were hypothyroid and 27 (44.9%) had euthyroid profile. 5 (8.3%) cases in secondary infertility group showed hypothyroid profile and 7 (11.05%) cases had euthyroid profile [Table 3].

It was observed that anovulatory cycles were present in 6 cases having thyroid dysfunction. Among 24 hypothyroid women 5(20%) were having proliferative endometrium suggestive of anovulation. While 18(72%) with secondary endometrium indicative of ovulatory cycles. Out of 2 hyperthyroid women 1 (4%) revealed proliferative anovulation and 1 (4%) had secretary suggestive of ovulatory cycles [Table 4].

Table 1. Distribution of cases according to study groups and age

Age group (in year)	Study group			Control group
	Primary infertility no. (%)	Secondary infertility no. (%)	Total no. (%)	No. (%)
20-25	21 (35%)	02 (3.33%)	23 (38.33%)	10 (25%)
26-30	20 (33.3%)	03 (5%)	23 (38.33%)	21 (52.4%)
31-35	05 (8.33%)	05 (8.37%)	10 (16.66%)	8 (20%)
> 35	02 (3.33%)	02 (3.33%)	04 (6.66%)	1 (2.5%)
Total	48 (80%)	12 (20%)	60 (100%)	40 (100%)

Table 2. Thyroid profile in study & control groups

Thyroid profile	Study groups			Control group
	Hyperthyroid	Hypothyroid	Euthyroid	Euthyroid
Serum FT3 (pmol/L)	21.33±7.31	3.52±1.20	4.19±0.58	4.17±0.80
Serum FT4 (pmol/L)	52.7±4.52	9.80±5.15	13.82±3.48	14.63±2.85
Serum TSH (µIU/ml)	0.22±0.10	21.98±19.86	2.16±1.24	2.72±1.57

*< 0.001*p value between hyperthyroid and control group; < 0.001**p value between hypothyroid and control group; > 0.05***p value between Euthyroid and control group*

Table 3. Relation of type of infertility and thyroid profile

Type of infertility	Hyperthyroid (%)	Hypothyroid (%)	Euthyroid (%)	Total
Primary infertility	02 (3.3%)	19 (31.66%)	27 (44.95%)	48 (80%)
Secondary infertility	----------	5 (8.33%)	7 (11.65%)	12 (20%)
Total	2 (3.3%)	24 (40%)	34 (56.6%)	60 (100%)

Table 4. Relation of abnormal profile and ovulation

Thyroid profile	Anovulatory cycle no. (%)	Ovulatory cycle no. (%)	Total (%)
Hyperthyroid	01 (4)	01 (4)	02 (8)
Hypothyroid	5 (20)	18 (72)	23 (92)
Total	06(24)	19 (76)	25(100)

4. DISCUSSION

The common endocrine disorders which result in infertility are hypothyroidism, hyperthyroidism, polycystic ovary syndrome diabetes mellitus, adrenogenital syndrome, Cushing's syndrome etc. Among these thyroid disorders are very important. Most of the studies available in literature have been done to find out infertility in cases of thyroid disorder, not the association of infertility with thyroid dysfunction, only few studies have been done so far [8,9].

In 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. Hypothyroidism (40%) was more prevalent than hyperthyroidism (3.3%).

The prevalence of thyroid dysfunction in infertile women was found to be 33.3% in a study by Rahman et al. [10] and 23% by Sharma et al. [9] in our study, hypothyroidism was present in 40 % and hyperthyroidism in 3.3% of infertile women. It is concluded that fertility of female reproductive system is altered by 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 infertile women is abnormally elevated TSH concentration ranges from 2-4% which found to be 6.7% by Rahman et al. [10], 8% by Goswami et al. [11], and 20% by Sharma et al. [9] while in our study this prevalence was 40%.

The abnormal hypothyroidisms disturb the ovulation and menstrual patterns. It is related to numerous interactions of thyroid hormones with the female reproductive system, and finally leading to infertility. In hypothyroidism, abnormally elevated TRH production leads to hyperprolactinaemia and altered GnRH pulsatile secretion. The hyperprolactinaemia is due to abnormal thyroid hormone secretion lead to delay in luteinizing hormone response and inadequate corpus luteum. The sensitivity of ovaries to thyroid hormones could be explained by the presence of hormone receptors in human oocytes. Thyroid hormones can act in conjunction with FSH-mediated LH/hCG receptors to stimulate granulose cells leading to the secretion of progesterone and abnormal TSH levels have been reported. In women who produced oocytes that could not been fertilized among patient undergoing in vitro fertilization. Hypothyroidism can also impact on fertility by changing the peripheral metabolism of estrogen and by reducing steroid hormone binding globulin secretion [12-15].

Thyroid dysfunction is a one of the common cause of infertility in women, which can be easily managed by appropriate thyroid hormones levels. In our data there are variations in TSH levels in the narrower range but it should not be ignored in infertile women who are otherwise asymptomatic for clinical hyperthyroidism. For better management of infertility case, we should plan further studies.

5. CONCLUSION

Infertility is a complex disorder that in a quarter of the couples is due to a female cause. Thyroid hormones play an important role in normal reproductive function, both through direct effects on the ovaries and also indirectly by multiple interactions with other sex hormones. Therefore, thyroid dysfunction can lead to menstrual irregularities and, thus, finally to infertility.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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