

Original Research Article

TITLE: STUDY OF THYROID DYSFUNCTION IN ASSOCIATION WITH INFERTILITY.

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 significant), 4.17 ± 0.80 pmol/L, when compared with control. FT₄ 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 μ IU/ml, in hypothyroid 21.98 ± 19.86 μ IU/ml (P value < 0.001 , i.e. significant), 2.61 ± 1.24 μ IU/ml in euthyroid (P value > 0.05 , i.e. not significant); 2.72 ± 1.51 μ IU/ml when compared with control.

Conclusion: Evaluation of thyroid status in the infertile couple is not only important because it is significant & most common but also its treatment is very simple & often has reversible or preventable effect on infertility.

Key words: Thyroid dysfunction, Infertility, Hypothyroidism, hyperthyroidism.

1. INTRODUCTION:

Infertility is the inability of a couple to conceive after one year of unprotected intercourse. It's prevalence is estimated to be 10-15% in any community. 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.^(1,2,3)

Endocrine system is the second key regulator of organ system function after nervous system in human body. Hormones are actually messengers in endocrine signaling. Thyroid gland holds a critical place in controlling brain & somatic development in infants & metabolic activities in adults upon stimulation by thyroid gland secretes thyroid hormones; triiodothyronine (T_3) & thyroxine (T_4) although thyroid hormones have a central 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 couple, is not only important because it is significant & most common but also its treatment is very simple & often has reversible or preventable effect on infertility.

2. MATERIAL & 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. 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 450nm. 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 450nm.

All the three parameters were estimated by following the same standard protocol provided by the manufacture (M/S Biomerieux).^(11,12,13)

2.3 Criteria of thyroid dysfunction :-

Thyroid function is considered normal (Euthyroid) when subjects were presented with normal T₃, T₄ & TSH. Abnormal thyroid function was further categorized as hyperthyroid (increased T₃, T₄ & decreased TSH). Subclinical hyperthyroid (increased T₃, T₄ & normal TSH). Hypothyroidism (decreased T₃, T₄ & increased TSH), & subclinical hypothyroidism (decreased T₃, T₄ & normal 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 profile (serum T₃, T₄ & TSH) in infertile women”, 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 no.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 no. 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 No.2]

Serum FT₄ 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

115 compared with control group 60(100%) women were in euthyroid range with serum T4 14.63 ± 2.85
116 pmol/L . [Table No.2]

117 Serum TSH level in 2(3.3%) hyperthyroid women was 0.22 ± 0.10 μ IU/ml (P value < 0.001, i.e.
118 significant); 21.98 ± 19.86 μ IU/ml in 24(40%) hyperthyroid women (P value < 0.001, i.e. significant), 2.61
119 ± 1.24 μ IU/ml in 34(56.6%) euthyroid group women (P value > 0.05, i.e. not significant; When compared
120 with control group 60(100%) women who had serum TSH levels 2.72 ± 1.51 μ IU/ml. [Table No.2]

121 Out of 48 patients of primary infertility, 2(3.3%) were hyperthyroid, 19(26.2%) were hypothyroid and 27
122 (44.9%) had euthyroid profile. 5(8.3%) cases in secondary infertility group showed hypothyroid profile and
123 7(11.05%) cases had euthyroid profile. [Table no. 3]

124 It was observed that anovulatory cycles were present in 6 cases having thyroid dysfunction. Among 24
125 hypothyroid women 5(20%) were having proliferative endometrium suggestive of anovulation. While
126 18(72%) with secondary endometrium indicative of ovulatory cycles. Out of 2 hyperthyroid women 1(4%)
127 revealed proliferative anovulation and 1 (4%) had secretary suggestive of ovulatory cycles. [Table no.4]

128 **Table No. 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%)

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130 **Table No. 2: Thyroid profile in study & Control groups**

Thyroid profile		Study groups		Control group	P value
	Hyperthyroid	Hypothyroid	Euthyroid	Euthyroid	
Serum FT3 (pmol/L)	21.33 ± 7.31	3.52 ± 1.20	4.19 ± 0.58	4.17 ± 0.80	< 0.001* < 0.001** > 0.05***
Serum FT4 (pmol/L)	52.7 ± 4.52	9.80 ± 5.15	13.82 ± 3.48	14.63 ± 2.85	< 0.001* > 0.05** > 0.05***
Serum TSH (μ IU/ml)	0.22 ± 0.10	21.98 ± 19.86	2.16 ± 1.24	2.72 ± 1.57	< 0.001* < 0.001** > 0.05***

*p value between hyperthyroid and control group

**p value between hypothyroid and control group

***p value between Euthyroid and control group

Table No. 3 Relation of type of Infertility and Thyroid profile

Sr. no.	Type of Infertility	Hyperthyroid (%)	Hypothyroid (%)	Euthyroid (%)	Total
1	Primary infertility	02(3.3%)	19(31.66%)	27(44.95%)	48(80%)
2	Secondary infertility	-----	5(8.33%)	7(11.65%)	12(20%)
	TOTAL	2(3.3%)	24(40%)	34(56.6%)	60(100%)

Table No. 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:

Female infertility occurs in about 37% of all infertile couples and ovulatory disorders account for more than half of these. Thyroid hormone has 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 increased than normal reference ranges. TSH levels are low or suppressed in subclinical hyperthyroidism and elevated in subclinical hypothyroidism. Recent data indicate that variation of free T4 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.^(5,6)

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%) in our study. This is in accordance with the report of Singh et al.⁽¹⁰⁾

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.⁽⁶⁾ in our study, thyroid dysfunction was present in 40 % of 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 abnormally elevated TSH concentration ranges from 2-4% which found to be 6.7% by Rahman et al., 8% by Goswami et al.⁽¹⁵⁾, and 20% by Sharma et al.,⁽⁶⁾ while in our study this prevalence was 40%.

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 hormone 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). 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 pituitary level.^(7,8,9)

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, 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.

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. We propose the systematic screening of infertile women for thyroid dysfunction, especially when endometriosis or ovarian dysfunction is the cause of infertility.

Further research is needed to answer crucial issues such as why thyroid autoimmunity is more linked to certain type of infertility.

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