International Journal of Research and Review
www.gkpublication.in E-ISSN: 2349-9788; P-ISSN: 2454-2237

Original Research Article

Thyroid Dysfunction and Possible Role of Anti-TPO in Infertility

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Received: 18/04/2016 *Revised: 22/04/2016* *Accepted: 25/04/2016*

ABSTRACT

Introduction: Thyroid autoimmunity is related to recurrent miscarriages as well as primary and secondary infertility. Infertility and reproductive outcomes can occur if there are abnormalities in both the endocrine and the immune systems by thyroid hormones and thyroid antibodies.
Aims and Objectives: 1) To study the association between anti-thyroid peroxidase antibodies and infertility among female patients, 2) To determine the correlation between anti-TPO antibodies, and T_3, T_4, TSH levels in females with infertility.
Materials and Methods: Cross-Sectional study was done from Jan. 2015 to Dec. 2015. 100 infertile females and 100 age-matched controls were selected. Serum anti-TPO antibodies, T_3, T_4 and TSH levels were evaluated.
Results and Discussion: Out of 100 infertile patients, 39 were of primary and 61 had secondary infertility, out of which anti-TPO Ab was elevated in 55 cases. An increase in the amount of anti-TPO Ab with age was seen. Highly significant increase of TSH and anti-TPO Ab levels was found in cases of primary infertility. Highly significant increase in T_4 and anti-TPO Ab levels was seen in secondary infertility. Pearson's correlations of T_3 with T_4, T_4 with TSH, TSH and anti-TPO Ab with duration of infertility, anti-TPO Ab with infertility were highly significant, T_3 with TSH, anti-TPO Ab with T_3, TSH with age, T_4 and TSH with infertility were significant.
Summary and Conclusion: Autoimmunity and thyroid disturbances are related with infertility. Anti-TPO Ab is independently associated with infertility irrespective of thyroid hormones levels and can be used for screening as well as the marker for identifying the risk factor of infertility.

Key Words: TPO-Ab, Infertility, Autoimmunity, Thyroid.

INTRODUCTION

Infertile females show a greater prevalence of thyroid autoimmunity as compared to normal fertile subjects. Several studies suggest that spontaneous miscarriage is increased in women who are positive for thyroid peroxidase antibodies (TPO-Ab), regardless of their thyroid function status. Thyroid autoimmunity (TAI) is related to recurrent embryo implantation failure, recurrent miscarriages as well as primary and secondary infertility. In all of these, anti-thyroid antibodies are suggested to be independent marker. [1]

Infertility is defined as the inability to conceive after 1 year of regular intercourse without contraception. [2] Infertility is considered primary if participation of either partner doesn't turn out to be successful in achieving pregnancy. Secondary infertility relates to couples who have achieved a pregnancy previously but are having difficulty currently with conception. [3,4]

In India, evidence on the prevalence of infertility is sparse and dated. The World Health Organisation's (WHO) estimates of primary and secondary infertility in India are 3% and 8%, respectively (WHO 1980, 1984). Data extrapolated from WHO by the Indian Council of Medical Research (ICMR) suggest that approximately 13-19 million couples are likely to be infertile in India at any given time (ICMR and NAMS 2005). [5] According to the National Family Health Survey in India, 3.8% of women aged between 40 and 44 were reported to be childless (IIPS 2000). [6] Infertility management has been evaluated carefully in the last decade as new medical and assisted reproductive techniques have gained widespread approval. [7]

Autoantibodies alter thyroid gland function by cellular damage which occurs when sensitized T-lymphocytes and/or autoantibodies bind to thyroid cell membranes leading to cell lysis and inflammatory reactions. Alterations in thyroid gland function result from the action of stimulating or blocking autoantibodies on cell membrane receptors. Measurement of circulating autoantibodies against thyroid antigens is of major importance in the evaluation of patients with various thyroid diseases since 1956, when Ivan Roitt first demonstrated their presence in patients with Hashimoto's disease. It was later demonstrated that one of the most important antigens is thyroperoxidase (TPO) enzyme which catalyses the deiodination of thyroglobulin and coupling of tyrosine residues to produce T_4 and T_3. Three principal thyroid autoantigens are involved in autoimmune thyroid disease (AITD), they are thyroperoxidase, thyroglobulin (Tg) and the thyroid stimulating hormone receptor (TSH receptor). [8] Out of these three, our study is based on antibody to thyroperoxidase. One mechanism by which these antibodies can cause infertility, abortion or congenital abnormalities in the foetus, is that they can directly bind to thyroid proteins which are important for thyroid hormone synthesis and release, leading to consequent reduction in serum levels of thyroid hormones. [9-11]

Aims and Objectives

1. To study the association between anti-thyroid peroxidase antibodies and infertility among female patients attending Gynaecological OPD of M.M.I.M.S.R. for the management of infertility.
2. To determine the correlation, if any, between anti-TPO antibodies, and T_3, T_4, TSH levels in females with infertility.

MATERIALS AND METHODS

The present study was cross-Sectional study conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, M.M.I.M.S.R, Mullana, Ambala period of one year from Jan. 2015 to Dec. 2015. 100 infertile females (primary as well as secondary infertility) and 100 age-matched non-pregnant females as controls were selected for the study who was attending the Gynaecological OPD for the management of infertility. Serum anti-TPO antibodies, T_3, T_4 and TSH levels were evaluated in all the selected patients and controls

The normal ranges of Serum T_3, T_4, TSH and anti-TPO antibodies were taken as: 0.52 - 1.85 ng/ml, 4.4 - 11.6 µg/dl, 0.28 - 6.82 µIU/ml and 6.82 - 28.4 IU/ml respectively. Serum T_3 and T_4 levels were estimated by ELISA (Competitive Enzyme Immunoassay), serum TSH and anti-TPO were determined by ELISA (Immunoenzymatic assay) methods as described by Sterling L. [12]

RESULTS AND DISCUSSION

In our study out of 100 infertile patients, 39 (39%) were of primary infertility and 61 (61%) had secondary infertility as shown in fig 1. Out of 100 cases, anti-TPO Ab was elevated in 55 cases. In 55 positive cases 23 were of primary infertility and 30 cases were of secondary infertility.

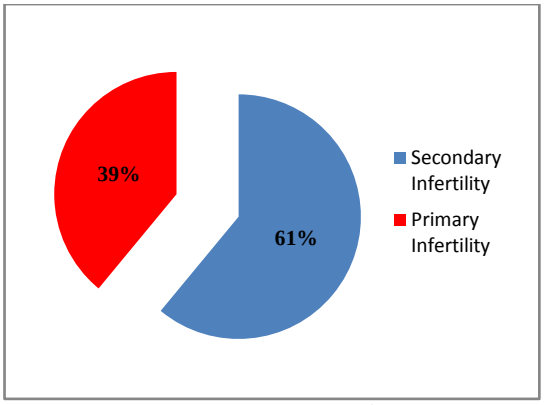

Fig- 1: Primary and Secondary Infertility cases

Age distribution of the women of both the groups varied between 18-45 years and maximum women were of the age group of 26-35 years. Maximum women were of secondary infertility (61 out of 100) and out of 61 women, 36 were falling in group of 26-35 years. In addition, an increase in the amount of anti-TPO Ab with age was seen. Our findings are consistent with findings of Kontiainen et al. [13]

Table 1: Mean value, standard Deviation and p value of anti-TPO Ab, T3, T4 and TSH in Primary Infertility cases and Controls.

	Groups	No.	mean±SD	p value
Anti - TPO Ab	Cases	39	65.31±110.0	<0.01**
	Controls	39	16.37±7.75	-
T_3	Cases	39	1.23±0.56	0.393
	Controls	39	1.32±0.27	
T_4	Cases	39	7.7±3.07	0.132
	Controls	39	10.39±10.25	
TSH	Cases	39	4.2±3.81	<0.01**

Mean value, standard deviation and p value of T_3, T_4, TSH and anti-TPO Ab in Primary Infertility Cases and Controls was studied as shown in Table-1. Mean TSH in cases and controls was 4.2±3.81 µIU/L and 2.3±1.32 µIU/L respectively. Mean anti-TPO Ab levels in cases and controls were 65.31±110.0 and 16.37±7.75 respectively. Highly significant increase of both TSH and anti-TPO Ab levels were found (p values <0.01) in cases of primary infertility.

Mean value, standard deviation and p value of T_3, T_4, TSH and anti-TPO Ab in secondary Infertility Cases and Controls was studied as shown in Table-2. Mean T_4 in cases and controls were 8.91±2.38 µg/dl and 8.02±2.6 µg/dl resp. Mean anti-TPO Ab levels of cases and controls were 47.6±75.6 IU/ml and 15.4±7.02 IU/ml resp. Highly significant increase in T_4 ($p<0.05$)and anti-TPO Ab levels ($p<0.01$)was seen in secondary infertile group as compared to control group.

Table 2: Mean value, standard Deviation and p value of anti-TPO Ab, T3, T4 and TSH in Secondary Infertility cases and Controls.

	Groups	No.	mean ± SD	p value
Anti - TPO Ab	Cases	61	47.64±75.6	<0.01**
	Controls	61	15.4±7.02	
T_3	Cases	61	1.20±0.54	0.284
	Controls	61	1.10±0.52	
T_4	Cases	61	8.91±2.38	<0.05*
	Controls	61	8.02±2.60	
TSH	Cases	61	2.56±3.14	0.069
	Controls	61	3.96±5.03	

Table 3: Mean value, standard Deviation and p value of anti-TPO Ab, T3, T4 and TSH in Infertility Total cases and Controls.

Groups		No.	mean±SD	p value
Age	Cases	100	28.49±5.22	<0.05*
	Control	100	30.12±5.85	
T_3	Cases	100	1.22±0.55	0.676
	Control	100	1.19±0.45	
T_4	Cases	100	8.47±2.7	0.514
	Control	100	8.95±6.77	
TSH	Case	100	3.22±3.50	0.815
	Control	100	3.34±4.08	
Anti-TPO Ab	Cases	100	54.53±90.51	<0.01**
	Controls	100	15.50±6.44	

Mean values, Standard Deviations and p values for total cases and controls were studied as shown in Table-3. Mean anti-TPO Ab in total cases (both primary and secondary infertile) and controls were 54.53±90.51 and 15.50±6.44 IU/ml resp and were found to be significantly ($p<0.01$) increased.

Pearson's correlation among the different parameters i.e. T_3, T_4, TSH, anti-TPO Ab, infertility, duration of infertility and age in cases was found out as shown in Table-4.

When we compared T_3 in cases with other parameters, Pearson's correlations (r values) of T_3 with T_4 was 0.372, highly significant (<0.01), T_3 with TSH was -0.210, significant (<0.05) and anti-TPO Ab with T_3 was 0.218, significant (<0.01).

When we compared T_4 in cases with other parameters, Pearson's correlations (r values) of T_4 with T_3 was 0.372, highly significant (<0.01), T_4 with TSH was -0.424 highly significant (<0.01) and T_4 with infertility was 0.203, significant (<0.05).

TABLE 4: Pearson's Correlations (r) between different parameters in cases

		T_3	T_4	TSH	TPO	Infertility	DOF	Age
T_3	**r**	1	0.37**	-0.21*	0.22*	-0.031	-0.03	-0.130
	Sig.		0.00	0.03	0.03	0.759	0.769	0.198
	No.	100	100	100	100	100	100	100
T_4	**r**	0.37**	1	-0.42**	0.134	0.20*	-0.138	-0.001
	Sig.	0.00		0.00	0.185	0.04	0.170	0.992
	No.	100	100	100	100	100	100	100
TSH	**r**	-0.21*	-0.42**	1	0.134	-0.23*	0.32**	0.23*
	Sig.	0.04	0.00		0.184	0.02	0.01	0.02
	No.	100	100	100	100	100	100	100
TPO	**r**	0.22*	.134	0.134	1	-0.096	0.22*	0.178
	Sig.	0.03	.185	0.184		0.344	0.028	0.07
	No.	100	100	100	100	100	100	100
Infertility	**r**	-0.03	0.20*	-0.23*	-0.096	1	0.22*	0.17
	Sig.	0.76	0.04	0.019	0.344		0.02	0.08
	No.	100	100	100	100	100	100	100
DOF	**r**	-0.03	-.138	0.32**	0.22*	-0.22*	1	0.63**
	Sig.	0.77	.170	0.001	0.028	0.022		0.00
	No.	100	100	100	100	100	100	100
Age	**r**	-0.13	-.001	0.23*	0.178	0.174	0.62**	1
	Sig.	0.20	.992	0.01	0.076	0.083	0.00	
	No.	100	100	100	100	100	100	100

When we compared TSH in cases with other parameters, Pearson's correlations (r values) of TSH with infertility was -0.235, significant (<0.05), TSH with duration of infertility was 0.320, highly significant (<0.01). TSH with age was 0.236, significant (<0.05).

When we compared anti-TPO Ab levels in cases with other parameters, Pearson's correlations (r values) of anti-TPO Ab with T_3 was 0.218, significantly increased (<0.05), anti-TPO Ab with duration of infertility was 0.220, significant (<0.05) and with infertility -0.302, highly significant (0.01). Interestingly, in our study we found a significant increase in antithyroid antibody titres in infertile patients, which was mainly anti-TPO Ab.

In 2009, according to Italian researchers, "Anti-thyroid antibodies, even if not associated with thyroid dysfunction, are suspected to cause a poorer outcome of, in vitro fertilization." In 1990s in various studies it was suggested that euthyroid women who presented with thyroid antibodies (thyroid peroxidase and thyroglobulin) in the first trimester of pregnancy have a two to four-fold increase in their miscarriage and infertility rates. [14]

Infertility and reproductive outcomes can occur if there are abnormalities in both the endocrine and the immune systems by thyroid hormones and thyroid antibodies. [15] Thyroid dysfunction has been recognized as one of the important causes in wide variety of gynaecological disorders such as abnormal sexual development, menstrual disorders, anovulation, infertility and reproductive failure as well as miscarriages. [16] Thyroid stimulating hormone (TSH) affects fertility by altering oestrogen metabolism and decreasing Serum hormone binding globulin production. In both pathways there is abnormal feedback at the pituitary level. [11] Hypothyroidism is also one of the causes of reproductive disorders ranging from menstrual irregularities to infertility and miscarriages. [15]

Since long it is being studied that maternal thyroid hormone whether they are in excess or deficiency may influence both mother and fetus in all stages of pregnancy. If there is maternal thyroid dysfunction in pregnancy it may cause fetal loss, pregnancy-induced hypertension, preterm delivery, placental abruption, and reduced intellectual function in the offspring.

Sieiro Netto et al studied that in women with higher in anti-TPO Ab and higher TSH levels are at risk of infertility and recurrent pregnancy loss. [17]

In the most studies for determining the relationship between autoantibodies and miscarriage, both of anti-TPO and anti-Tg

antibodies have been measured, in addition to TSH level and FT_4 level.

Our results were in agreement with other researchers.

Stagnaro-Green et al found a relationship between thyroid autoantibodies and pregnancy loss. They studied that there is increase in miscarriage rate if women are positive with Anti-thyroid Ab compared to those with negative Ab ($p<0.01$, $p<0.001$), respectively. [18]

Bussen found that with presence of thyroid autoimmunity is related to infertility and miscarriages. In his study, he found out that there was increased prevalence of ATA (54.2%) in euthyroid women who went for with three or more (In vitro fertilization) IVF and resulted in IVF failure. [19] Interestingly, in our study also we found a significant increase in antithyroid antibody titers in infertile patients, which was mainly anti-TPO Ab. Lejeune et al also reported that the miscarriages have relation with Antithyroid Abs and may occur early in pregnancy that is in the first trimester of the pregnancy. [20] Several researchers studied that women with anti-TPO Ab and/or anti-Tg Ab had a higher miscarriage rate than women who were negative for these antibodies ($p<0.05$) respectively. [21] Potential theories for patho-physiological changes leading to infertility and recurrent pregnancy loss in women who carry thyroid autoantibodies include: 1) There may exist a subtle degree of hypothyroidism; 2) Thyroid autoantibodies directly cause recurrent spontaneous abortion; 3) Women with thyroid autoimmunity and subfertility become pregnant at older ages (often after 30 years), which by itself, may constitute an additional factor to explain the greater rate of abortion; 4) More frequent rejection of fetus and the presence of thyroid antibodies represent an epiphenomenon that points out an underlying overall autoimmune imbalance resulting in risk of recurrent spontaneous abortion. [18] In several studies it is suggested that presence of thyroid autoantibodies leads to generalized activation of the immune system particularly of T cells, and they are ultimately responsible for the loss of the pregnancy. [22]

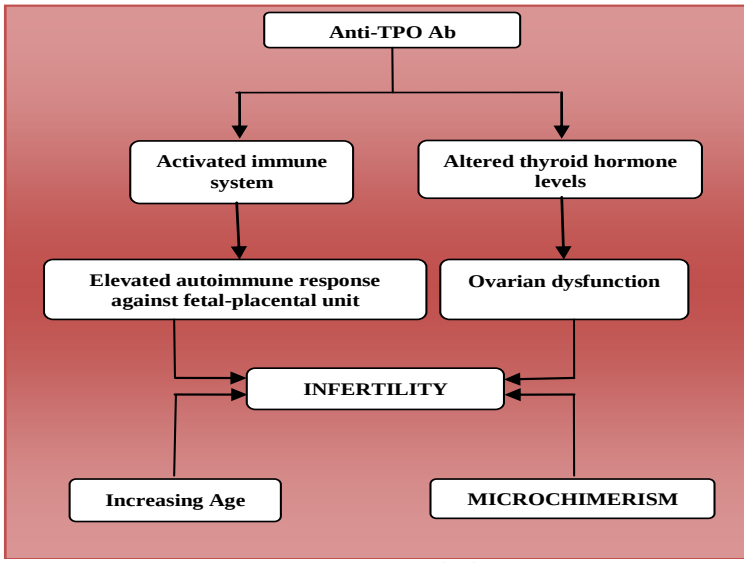

Fig- 2: Pathophysiology of infertility

In fetal microchimerism there is a mixture of maternal and fetal cells. There is increased transplacental passage of fetal cells into the maternal thyroid which explains an enhanced immune response against the fetoplacental unit. [23] (Figure-2)

Poppe K et al studied that abnormality in thyroid function itself is a condition which interferes with normal

ovarian function and was seen more frequently in women who were positive with anti-TPO Ab. He therefore, reported that if there should be systematic screening of TSH, thyroid hormones levels and anti-TPO Ab in all women with a female cause of infertility. [2] TAI is one of the most common autoimmune disorders that affect 5-20% of women in the childbearing period. TAI is also the main cause of thyroid dysfunction, even though thyroid autoimmunity can be present without hormonal dysfunction. [24] In early gestation many women with TAI frequently progress to hypothyroidism despite a euthyroid status, because maternal thyroid requirements are increased which cannot be met. Therefore, progressive hypothyroidism often develops or worsens as the gestation progresses. [25] Gartner R et al also suggested that women with euthyroid status have high thyroperoxidase antibodies more often lead to miscarriages. [26] Matalon ST et al also observed that women with euthyroid status and recurrent miscarriages are found to have increased levels of autoantibodies either against thyroglobulin or thyroperoxidase while the probability of abortion in women with ATA has been shown to be more than in control. [27] Marai et al studied that anti-TPO Ab were the only autoantibodies found to have a significantly associated with infertility and miscarriages. [28] Dendrinos S et al found out presence of anti thyroid antibodies were higher in women with unexplained infertility as compared to women with recurrent spontaneous abortion. [21,29] Rushworth studied in 870 consecutive women who had history of recurrent miscarriages that 19% of them were found to be positive for anti - TPO Ab. [30]

SUMMARY AND CONCLUSION

It is concluded from the present study that autoimmunity and thyroid disturbances are related with infertility. Anti-TPO Ab is significantly associated with infertility in women which shows that anti-TPO Abs are independently associated with infertility irrespective of thyroid hormones levels. In our study there were many female who did not have thyroid dysfunction but were found to be positive for anti-TPO Ab. Therefore, they may not be the cause but can be used as the marker for identifying the risk factor of infertility. Recent trials of thyroxine replacement and immunomodulatory drugs have shown positive results in normalizing thyroid function and reducing obstetrical complications. Given the possibility of effective intervention, screening for AITD in all women with infertility and miscarriage is recommended.

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How to cite this article: Manhas S, Mahajan S, Prasad S et al. Thyroid dysfunction and possible role of anti-TPO in infertility. Int J Res Rev. 2016; 3(4):39-45.

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