Antithyroid Autoantibody in Unexplained Recurrent Abortion

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ABSTRACT:

BACKGROUND:

Recurrent miscarriage is a common complication of pregnancy and when the cause is unknown; relationship of autoimmune thyroid disease to pregnancy loss has been the object of considerable interest.

OBJECTIVE:

To estimate whether thyroid auto-antibodies (thyroglobulin and thyroid peroxidase antibodies) could be used as a marker for detection of abortion in cases with unexplained recurrent miscarriage.

METHODS:

This study was carried out at the department of obstetrics and gynecology in AL- Kadhymia Teaching Hospital from March 2008 through September 2009. Fifty pregnant women in their first trimester (7^{th} – 12^{th} weeks) were followed up till 20^{th} weeks of gestation by the researcher himself (they have three previous unexplained first and second trimester miscarriages).Thyroid peroxidase (TPOAB) measurement by ELISA and thyroglobulin antibodies (TGAB) by slide methods with flourescein were done to the patients, cases with abortions were reported and the status of thyroid antibodies was evaluated. Free T3; free T4, TSH measured by RIA technique.

RESULTS:

In eighteen patients the antibody titer was positive while thirty-two had negative tests for thyroid auto-antibodies. TGABS (thirty-six) were negative, (thirty-three) continue pregnancy and only (three) aborted. TGABS (fourteen) were positive, (four) cases continue and (ten) aborted. TPOABS (forty-one) were negative (thirty-nine) cases continue pregnancy and only (two) aborted. TPOABS (nine) cases were positive, (seven aborted and only (two) cases continue pregnancy. This study showed a significant association between AB. Positivity and maternal age.

CONCLUSION:

Thyroid auto antibodies can serve as a useful biochemical marker for cases with unexplained recurrent miscarriage and there is a positive relation with increasing maternal age (thyroid auto antibodies).

***KEYWORDS*:** recurrent abortion, thyroid auto antibodies, tgabs and tpoabs.

INTRODUCTION:

Recurrent miscarriage is defined as three or more consecutive spontaneous miscarriage, it occurs in about o.5-3% of women trying to conceive. [1]

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Adaptation of the maternal immunological response is required for successful implantation of the embryo. This depends on a link between the fetal antigen presentation and maternal recognition and response to the antigen. Some studies have reported high levels of various auto antibodies in woman with recurrent miscarriage (RM) about 18-43%. The antibodies may affect pregnancy in two ways, either by a direct effect on fetal tissue or as a reflection of a more wide spread underlying autoimmune response. The prognostic value of thyroid antibodies has been studied, while some studies and investigation

found it a good prognostic marker, other studies did not. [2]

Autoimmune thyroid disorders characterized by the presence of auto antibodies against thyroid specific components such as thymoglobulin, thyroid peroxides and the thyrotrophic receptor in Graves' disease. However, to autoimmune thyroid disease, anti thyroglobulin (TGAB) and anti-thyroid peroxides (TPOAB) antibodies have been reported in many patients with non-thyroidal disease, and even in normal population. On the other hand, high prevalence of auto antibodies directed against non

thyroidal-specific antigens has been described in patients with autoimmune-thyroid disease. [3]

Thyroid auto antibodies have been shown to be useful markers in predicting women outcome for clinical miscarriage. The thyroid auto antibodies are common in the general population and at all ages are up to five times more common in women than in men. The tendency to secrete thyroid auto antibodies is inherited in a Mendelian dominant manner. [4]

Nearly all patients with Hashimoto's thyroditis have Abs to both TGA and TPO Abs, although these Abs are not specific for the disorder. [5]

Thyroid auto Abs is a secondary response to thyroid injury. Both types of Abs are poly and although of IgG class, are not restricted to one particular IgG sub class which both TPOAB, TGAB levels correlate with lymphocytic infiltration of the thyroid. They do not transfer disease from mother to fetus. [6]

Antithyroid antibodies reflect generalized activation of immune system. Stagnaro suggested that ABS are secondary markers of auto immune risk rather than specific causative factors, however the role of thyroid ABS positivity as a causative factor of abortion, still need more explanation.[4]

The study is aimed to test the value of measuring thyroid antibodies TGAB & TPOAB as predictors of abortion in those women with history of unexplained recurrent abortions.

PATIENTS AND METHODS:

This prospective study was carried out at the Department of Obstetrics and Gynecology in AL-Kadhymia Teaching Hospital from March 2008 through September 2009, a total of 50 pregnant women were included in the study, presented in the first trimester (from 7th till 12th) weeks of gestation of different ages, who had previously unexplained recurrent abortion.

The samples size were fifty pregnant ladies collected from outpatients' clinics and antenatal care clinics.

All patients were assessed clinically by history, clinical examination and investigations for the presence of thyroid diseases. Patients answered a questionnaire regarding thyroid illness, family history and related symptoms.

Exclusion Criteria

1. Patients with partner with abnormal karyotype.
2. Those with medical problems.
3. Antiphospholipids antibody syndrome.
4. Toxoplasmosis, cytomegalovirus and patients with VDRL positive.

All selected women were subjected to the following investigations:

Thyroglobulin antibodies (TGAB) and thyroperoxidase (TPOAB) by Elisa. Specimen collection (serum) was performed at the time of initial presentation.

Thyroperoxidase (TPO AB)

Anti TPO is an indirect solid phase enzyme immunoassay ELISA for the quantitative measurement of IgG class of auto-abs against (TPO) in human serum or plasma.

In a normal range study with serum samples from healthy blood donors, the following ranges have been established with anti TPO.

Test kit:-

Normal	Less Than 50	(Anti – TPO) IU/ml
Boarder Line	50 – 75	
Elevated	More Than 75	

Thyroglobulin antibodies (TG AB)

Auto antibodies against thyroglobulin react with the follicle of the thyroid tissues and cause articular fluorescence pattern.

If the cell nuclei or the cytoplasm of all cells are stained, anti-nuclear or abs. against mitochondria

and other cell antigen are present. The samples are from human sera.

Frozen sections of thyroid gland covering the reaction area of a (BIOCHIP) slide are incubated with diluted patient samples. If the reaction is positive, specific antibodies of classes IgA, IgG and IgM attached to the thyroid gland antigens.

The attached antibodies are stained with fluorecsein – labeled anti human antibodies and made visible with the fluorecsein microscope. No cross reactivity was described.

If the positive control shows no specific fluorecsein pattern or the negative control shows a clear specific fluorecsein, the results are not to be used and the test to be repeated.

Thyroid parameters were assessed by free T3, free T4 and TSH were measured by RIA technique. Follow up for all patients till 20th weeks of gestation was done and cases of abortion were reported.

Statistical Analysis

The student t test, fissure's exact test and Chi square. Statistical significant was defined as $p < 0.05$.

Positive predictive value and negative predictive value were used.

RESULTS:

Figure 1 showed a significant difference in age of cases with antibody positive and antibody negative tests. Those with antibody positive tests have older age group (30-39 year).

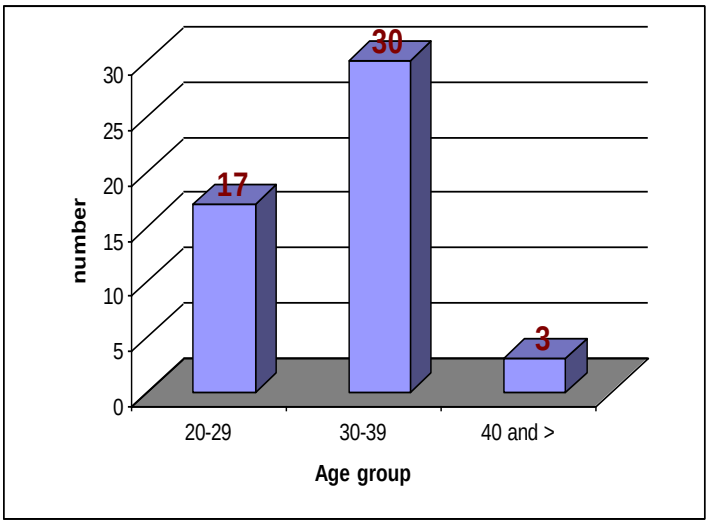

Fig. 1: Age distribution in relation to thyroid autoantibody positivity

Distribution of patients according to thyroid auto-antibody results:

Eighteen out of 50 (36 %) were positive for auto-antibody, while the rest of the patients were negative (32; 64%). Fig. 2

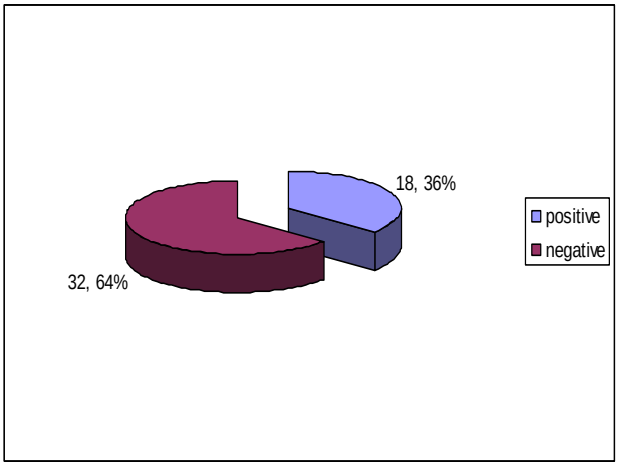

Fig. 2: Distribution of patients according to auto-antibody results

Figure 3 shows the distribution of patients during pregnancy till 20 weeks of gestation:

Seventeen out of 50 patients (34%) were aborted; and the rest of patient (33; 66%) continued till 20 weeks of pregnancy.

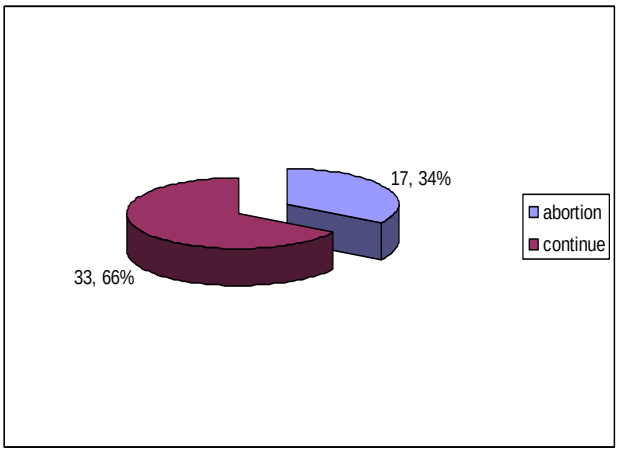

Fig. 3: Distribution of patients during pregnancy till 20 week of gestation

Out of 18 cases with antibody positivity, 12 cases (66.6%) had spontaneous abortion while 5 cases (15.6%) out of 32 women with antibody negative tests were aborted. The difference was highly significant. P value <0.001

Correlation between outcome of pregnancy and TGABS:

Table.1 showed a significant difference between those patients who continue till 20 weeks and the rest who aborted i.e. those who were positive for TGABS, were more liable to have abortion (10 out of 13); while those having negative TGABS were less liable to have abortion (4 out of 37). P value <0.001

Table. 1: Correlation between outcome of pregnancy and TGABS

		Outcome		
		Continue	Abortion	Total
TGABS	Negative	33	3	36
	Positive	4	10	14
	Total	37	13	50

Fischer exact test (p-value<0.001)

Correlation between outcome of pregnancy and TPOABS:

Table.2 showed a significant difference between those patients who continue till twenty weeks , above and the rest who aborted i.e. those who were positive for TPOABS, were more liable to have abortion (7 out of 9); while those having negative TPOABS were less liable to have abortion (2 out of 41). P value <0.001

Table 2: Correlation between outcome of pregnancy and TPOABS

		Outcome		
		Continue	Abortion	Total
TPOABS	Negative	39	2	41
	Positive	2	7	9
	Total	41	9	50

Fischer exact test (p-value<0.001)

DISCUSSION:

A number of studies have linked thyroid antibodies with recurrent abortions, although the mechanism involved is not clear. It is postulated that the presence of thyroid autoantibodies reflects a generalized activation of the immune system and a generally heightened autoimmune reactivity against the feto-placental unit.[4]

The present study showed that most of thyroid autoantibody positive women were in age group of 30-39 years. This is in agreement with a study of Kutteh et al, [7] who found a high number of patients with recurrent pregnancy loss demonstrated elevated antibody titer as age increased up until the age of 31-35 years. Other study done by Kontianen et al [8] found an increase in the titer of TPO Abs with age, but this correlation was not statistically significant.

The presence of thyroid autoantibodies may act as infertility factor and may delay conception. Thus, when women with thyroid autoantibodies do become pregnant, they were older and face a higher risk of miscarriage [9].

This study showed the incidence of thyroid antibody positivity was higher in aborters than in non aborters (66.6% vs. 15.6%) so the presence of thyroid autoantibodies may increase the risk of spontaneous abortion. This is in consistent with a study of Stagnaro-Green et al [4] who did screening of 552 women in the first trimester of pregnancy for thyroid autoantibodies, they were the first to report a doubling of the miscarriage rate in women who were antibody positive in the first trimester as compared to an antibody negative cohort (17% vs. 8.4%).The present study shows that 12 (66.6%) of 18 with thyroid antibody positive women and 5 (15.6%)of 32 thyroid antibody negative women had spontaneous abortion. This is in agreement with a study done by Pratt et al [10] in which pregnancy outcome was evaluated in 42 euthyroid women with history of three or more consecutive, first trimester abortions, 31% had thyroid autoantibodies, 8 of 13 thyroid autoantibody positive women and only 4 of 29 thyroid autoantibody negative women miscarried (62% vs. 14%, P=0.003). The authors concluded that in women with recurrent abortion, the presence of thyroid antibody positivity was associated with an increased risk of pregnancy loss in subsequent pregnancy.

The present study is not consistent with Rushworth et al [4] study who evaluated the pregnancy outcome of 24 antibody-positive euthyroid (TgAbs, TPO Abs, and both) women

with a history of recurrent abortion through a subsequent pregnancy. Eighty one thyroid antibody negative women with recurrent abortion served as controls. The live birth rate of the two groups was identical at 58%. They concluded that thyroid antibody positivity in women with recurrent abortion does not ported a worse outcome when compared to women who are thyroid antibody negative. This is may be due to the small number of thyroid antibody positive women evaluated. Other large scale study compared successful pregnancy in groups of women with recurrent abortion. They found that the group of women who were thyroid antibody positive had significantly lower rates of successful pregnancies than the group with negative thyroid antibody (57% vs. 92%) [(11)].

Other studies evaluated presence of thyroid autoantibodies in women with recurrent miscarriage. They found that thyroid antibody positivity rate was significantly higher in women with recurrent miscarriage compared to the controls[(12,13,14)].

It is obvious that the final goal of clinicians is to decrease miscarriage rate in women with thyroid autoimmunity to that of general population, so in order to prevent miscarriage, recently few studies shows that thyroxine administration to pregnant women with positive thyroid autoantibodies with or without history of recurrent miscarriage may be effective in reducing the number of miscarriages and improve the fetal outcome when given during the early stages of pregnancy [15, 16, 17]. Further studies are required with greater number of women in order to reach definitive conclusions.

CONCLUSION:

There was a significant relation between pregnant women with history of unexplained recurrent abortion who have positive thyroid auto antibodies and risk of spontaneous abortion compared to those who have not.

Assessment of thyroid autoantibodies can be used as a marker for cases with unexplained recurrent abortion.

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