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The Anti-Thyroglobulin and Anti-Thyroperoxidase Auto Antibodies Comparative Mean Titer Values In Infertile Compared To Ferlile Euthyroid Women

[1]* OLADIMEJI, S. O.; [2]MAGBAGBEOLA, O. A.; [2] AKINWANDE A.I.; AND
[3] VANDERPUYE, O.A.

1-Department of Biochemistry, Faculty Of Science, Lagos State University, Ojo, Lagos.
2-Department of Biochemistry College Of Medicine, University Of Lagos Idi-Araba, Lagos
3- Department of Forensic Science, Albany State University, Albany U.S.A.

ABSTRACT

OBJECTIVE: This study was carried out to determine the anti-thyroglobulin and anti-thyroperoxidase serum auto-antibody levels as primary markers and their immunological correlates as indicators of the cause of infertility and the recurrent spontaneous abortion in some Euthyroid Nigerian women.

DESIGN: A total of two hundred and ninety (290) Euthyroid female volunteers were recruited having filled a designed questionnaire to obtain their informed consents. Thereafter, following the Ethics group recommendations, blood samples were collected from each of the one hundred and sixty four (164) women in the control groups, a week after their menses. The control groups recruited are as follows: (46) nulligravida, (58) multiparous non-pregnant women and (60) pregnant women in their first trimester, served as the third control group. There were one hundred and twenty six (126) infertile women in the test group, made up of (34) primary infertile, (46) secondary infertile and recurrent spontaneous aborters respectively.
The assays of anti-thyroglobulin and anti-microsomal (thyroid peroxidase-anti-TPO) antibodies were determined, using individual agglutination kits and the diagnostic ELISA kits (enzyme linked immuno-sorbent assay) from meridian Bioscience Europe.

RESULT / OUTCOME: This study had therefore established the significant presence of anti-thyroglobulin and anti-thyroperoxidase as immune species marker in the serum of some Euthyroid Nigerian women experiencing reproductive failure compared to the women in the control group. The serum anti-thyroglobulin (Tg-Ab) and anti-microsomal (anti-thyroperoxidase (TPO- Ab) auto antibodies showed that serum anti-thyroglobulin (Tg-Ab) level was significantly higher in the women in the secondary infertile (809.65$\pm$ 3.23 U/ml) than that of the primary infertile group with 539.59$\pm$3.79 U/ml as well as the recurrent spontaneous aborter group with 490.00$\pm$3.20 U/ml. This are compared with the control women in the nulligravida with (42.48$\pm$3.16 U/ml), multiparous (32.02$\pm$ 2.82 U/ml) and the pregnant (31.90$\pm$ 2.77 U/ml) groups. The anti-thyroperoxidase (TPO-Ab) mean titer of the study group was equally higher and significant ($P < 0.05$) compared to the women in the control group.
Keywords: Anti-thyroglobulin (Tg Ab) , anti-thyroperoxidase (TPO Ab), pregnancy, primary infertility and Recurrent Spontaneous Abortions

1.1 INTRODUCTION

Anti-thyroglobulin autoantibody (TgAb) was the first auto-antibody to be implicated as involved in patients with autoimmune thyroid disease (AITD). Beever et al., (1989) used enzyme-linked immune-sorbent assay (ELISA) as an improved detection method over the agglutination technique to evaluate the auto-antibody (Kowalik et al., 1997). Anti-thyroglobulin autoantibodies are primarily of the IgG class with poor activators of complement cascade (Clark et al., 1991). The inability of TgAb to fix complement could not be explained by the skewness of their subclass distribution; there seems to be neither defined biological action nor patho-genetic importance attached to TgAb (Kutteh et al., 1999; Nussinovitch et.al., 2012).
Cowchock et al., (1992) opined that auto-antibodies may affect the maternal thyroid gland. The auto-antibodies crossing the placenta may affect the foetus, as seen in 40% of neonates born to mothers with elevated autoantibody levels. At birth, a newborn ought to have normal globulin and thyroid stimulating hormone (TSH) to the fifth day of life (Kwak et al., 1992). The potential importance of the presence of elevated antigen passively

transmitted from the mother remains to be clarified (Glinoer et al., 1991; Quintero et. al. 2012). However the gestational factors like anti-phospholipids may be affected, which causes decidua vascularity and placental insufficiency. And those thyroid auto-antibodies may be the result rather than the cause of recurrent pregnancy loss (Weetman and McGregor, 1994; Nussinovitch and Shoenfeld 2012). However, an interaction exists between thyrotrophic-like hormones produced by human placenta, human chorionic gonadotropin and the thyroid auto-antibodies resulting in early pregnancy loss (Singh et al., 1995).

Thyroid peroxidase autoantibodies (TPO) were first recognized by complement fixation and indirect immuno-fluorescent staining of fixed section of thyroid tissue and later by using heamaglutination assay technique (Kutteh et al., 1997). Regardless of the technique used, TPO Ab is present in the serum of almost all patients with thyroid disorder cases and in patients with thyroid autoimmune disease (Carreres and Mooney, 1992). Thyroid peroxidase antibodies in most serum samples react with both linear and conformational epitopes on enzyme antigen TPO, which is recognized by microsomal antibodies. It seems likely that the TPO Ab arose as a consequence of thyroid damage with limited biological importance, but is an excellent marker of the underlying autoimmunity (El-Roeiy and Gleicher, 1988; Coulam et al., 2006,).

Women with antithyroid antibodies (ATA), face double risk of miscarriage as against women without them (Geva et al., 1997). Increased thyroglobulin and thyroid-microsomal (thyroperoxidase) auto-antibodies level show relationship to an increased miscarriage rate. About 31 percent of women experiencing recurrent spontaneous abortion (RSA) are positive to one or both antibodies (Coulam, 1992). The chance of a loss in the first trimester pregnancy increases to 20 percent, and there is also an increased risk of post partum thyroid dysfunction (Gleicher et al., 1992; Fairweather et al., 2012).

In 1990, Stagnaro-Green et al., demonstrated in a prospective analysis that thyroid antibodies were markers for "at-risk" pregnancies. The two antibodies studied, anti-thyroid peroxidase and anti-thyroglobulin antibodies, are collectively referred to as anti-thyroid antibodies (ATA). Many reports have since corroborated the markedly increased prevalence of ATA in women who experience reproductive failure, especially first trimester miscarriages. Pratt, et al., (1998), showed that 67% of women with recurrent first trimester losses had ATA, compared to 17% of controls. None of the participants in either group had clinical manifestations of thyroid disease.

This study was carried out to provide the base line information on the African women immune reproductive assessment of some volunteer Nigerian women with recurrent spontaneous abortions (RSA) and infertility of immune etiology.

1.2. RESEARCH METHODS

1.2.1SUBJECTS: Two hundred and ninety (290) women volunteers were recruited and took part in this study. Of these, one hundred and twenty six (126) patients were from the obstetrics and gynaecology unit of Ayinke house at the Lagos State University Teaching Hospital, were grouped as the test subjects. Thirty four (34) women were grouped as diagnosed as experiencing Primary infertility, forty six (46) women were grouped into secondary and recurrent spontaneous aborter respectively. The one hundred and sixty four (164) women were recruited in the control groups, which include; forty six (46) Non-pregnant Nulligravida women volunteers and fifty eight (58) multiparous non-pregnant women volunteers recruited. Sixty (60) pregnant women that undergone antenatal care at the antenatal ward of Ayinke House of the Lagos State University Teaching Hospital., Ikeja, were recruited. The exclusion factors include women that are hypertensive, experiencing thyroid diseases or on hormonal balancing drugs were ruled out. The study was conducted according to the ethical standard of the research and ethics committee of the Lagos State University Teaching Hospital.

1.2.2 BIOLOGICAL SAMPLES: Venous blood sample was collected in triplicate into plain tubes of 10 ml each from the two hundred and ninety volunteers. The serums obtained after samples were allowed to stand for an hour and then centrifuged at 400prm for 10 minutes were stored at -4^0C until needed for analysis.

1.2.3 EXPERIMENTAL PROCEDURE: The frozen serum samples were brought to room temperature and tested for positivity to anti-microsomal auto-antibodies (anti TPO) in both the test group and the control groups using a commercially available Agglutination and Enzyme linked immuno-absorbent assay (ELISA) kits.

Positive results of antiTPO antibody concentration are defined as titers greater than or equal to the benchmark of the normal level (of ≥ 40 U/ml). The bench marks for the determination of the anti-Tg level that was above normal level, of ≥ 200 Unit /ml., according to the manufacturers instruction (Meridan Bioscience Europe)

Statistical analysis was carried out using the mean and standard deviation and the analysis of variance (ANOVA) Package and the correlation analysis on the SPSS v.11 electronic statistical tools of windows www.spss.com

1.3. ANALYSIS RESULT:

1.3.1 The agglutination evaluation: Table 1 shows the agglutination evaluations result, that showed the presence of anti-thyroglobulin (Tg Ab) and anti-thyroperoxidase (TPO Ab) antibodies in the serum of control and test groups. The result established the presence of auto antibodies to thyroglobulin (Tg Ab) with the highest number in the women in the primary infertile group of 86% and 75% in the RSA group. The anti-thyroperoxidase was found in 80% of women in the infertile group and 79% in the RSA group ie among the women experiencing reproductive failure.

Table 1: AUTO-ANTIBODY IMMUNOPHENOTYPIC AGGLUTINATION VALUES OF Tg Ab AND TPO Ab OF CONTROL AND TEST GROUPS

AGGLUTINATION (Euthyroid Women) Tg Ab and TPO –Ab	**CONTROL GROUP (Nulligravida) Tg Ab N=26 (46) TPO–Ab N=23 (46)**	**TEST GROUP** Primary infertile N=28 (34)	**TEST GROUP RSA N=33 (46)**
Tg-Ab ++	2 (8%)	24 (86%)	25 (75%)
Tg-Ab +	5 (19%)	4 (14%)	7 (22%)
Tg-Ab -	19 (73%)	0	1 (3%)
ND	20	6	13
TPO-Ab ++	1 (4%)	22 (80%)	26 (79%)
TPO-Ab +	3 (13%)	4 (15%)	7 (21%)
TPO-Ab-	19 (83%)	2 (5%)	0
ND	23	6	13

Note: The figures in the table represent numbers of women in the control and test groups.
KEY: ++ve - Strongly positive +ve - slightly positive -ve - negative ND - not determined.

1.3.2 The serum anti-thyroglobulin and thyroperoxidase auto-antibody mean titer values:

The obtained mean titer values of the autoimmune species of anti-thyroperoxidase (anti-TPO), considered to be positive were those values that were above the benchmark of the normal level (of < 40 U/ml). The results in Table 2 showed that within the control group, the multiparous women had higher serum anti-TPO positive mean titer value of 76.01 ± 0.97 Unit/ml compared to others, having anti-TPO negative within the normal range. Comparing also the serum anti-TPO positive mean titer of 88.88 ± 1.35 Unit /ml of the women in the nulligravida group and 62.50 ± 0.90 Unit /ml in the pregnant group, within the control groups, compared with that of the negative anti-TPO of the other control group there was no significant difference at $P < 0.05$. Whereas, comparing the mean titer of 1503.50 ± 1.16 Unit /ml in the primary infertile women and 747.41 ± 0.99 Unit /ml in the recurrent spontaneous aborter and 613.39 ± 0.99 Unit /ml in the secondary infertile women against control groups, they were significantly higher at $P < 0.05$. The anti-thyroperoxidase anti-TPO negatve mean titer values obtained in the control group showed that, the women in the nulligravida group had 22.48 ± 1.47 Unit /ml, the multiparous group had 33.60 ± 1.31 Unit /ml and the pregnant group had 33.50 ± 3.37 Unit /ml . They were all within the normal range.

The mean serum titer value of the anti- throglobulin (anti- Tg) in the women studied are as shown in Table 2. The bench marks for the determination of the anti-Tg level that was above normal level, of < 200 Unit /ml. The anti- Tg values were all negative, in the women of the control group with 42.48 ± 3.16 Unit /ml in the nulligravida group, 32.02 ± 2.82 Unit /ml in the multiparous group and 31.90 ± 2.77 Unit /ml in the pregnant group. The titer value in the test group positive to anti-Tg was 539.59 ± 3.79 Unit /ml in the primary infertile, 809.65 ± 3.23 Unit /ml in the secondary infertile and 490.00 ± 3.20 Unit /ml in the spontaneous aborter group. These was significantly higher at $P<0.05$ than the negative anti-Tg in the control group, as well as within the test group with negative anti-Tg of 144.00 ± 15.17 Unit /ml in the primary infertile, 138.00 ± 15.17 Unit /ml in secondary infertile and 122.00 ± 21.45 Unit /ml in the spontaneous aborter group.

TABLE 2 : COMPARATIVE ANALYSES OF SERUM THYROGLOBULIN AND THYROPEROXIDASE AUTO ANTIBODY ELISA VALUES OF THE WOMEN STUDIED.

	Overall marginal mean /Number of Women with		**Mean TgAb (unit/ml)**		**Mean TpoAb (unit/ml)**		**Age range (years) / Duration of years of**	
PARAMETERS N=290	Anti-Tg	Anti-TPO	Anti-Tg(-) N=169	Anti-Tg(+) N=121	Anti-TPO(- N=35	Anti-TPO(+) N=255	Age range	Duration
CONROL GROUP Nulligravida Women	42.48 ± 3.16 n=46	55.68 ± 1.00 n=46	42.48 ±3.16 n=46	n=0	22.48 ±1.47 n=21	88.88±1.35 n=25	20-50	-
Multiparous Women	32.02 ± 2.82 n=58	54.81 ± 1.17 n=58	32.02 ±2.82 n=58	n=0	33.60 ±1.31 n=10	76.01 ±0.97 n=48	20-28	-
Pregnant Women	31.90 ± 2.77 n=60	48.00 ± 1.74 n=60	31.90 ±2.77 n=60	n=0	33.50 ±3.37 n=4	62.50 ±0.90 n=56	20-46	-
TEST GROUP Primary Infertile Women	341.80 ± 7.82 n=34	1503.50 ±1.16 n=34	144.00±15.17 n=.2	539.59±3.79 n=32	n=0	1503.50±1.16 n=34	20-48	2-17
Secondary Infertile Women	473.82 ± 7.75 n=46	613.39 ± 0.99 n=46	138.00±15.17 n=2	809.65±3.23 n=44	n=0	613.39 ± 0.99 n=46	21-48	0.5-10
Recurrent Spontaneous aborter	306.00±10.84 n=46	747.41 ± 0.99 n=46	122.00±21.45 n=1	490.00±3.20 n=45	n=0	747.41 ± 0.99 n=46	20-39	1-8

Data are expressed as mean ± SE and analyzed by ANOVA (Two-way test) $P<0.05$ – significant [a]$P<0.05$ comparing Anti-Tg/ Anti-TPO positive vs negative, [b]$P<0.05$ infertile women vs control group.

1.4. DISCUSSION

This study on the African- Nigerian women immune reproductive assessment provide a data base line results on recurrent spontaneous abortions (RSA) and infertility of immune etiology. The volunteer women in this study

were grouped into the age brackets classified into early and late marriages, as recruited from among the women attending the various clinics visited, that were within the reproductive age brackets, see Table 1and 2. The reproductive age of an average woman in general, is put between 16 – 45 years, which represents the reproductive events between puberty and menopause. The age distribution in Table 2, showed that the majority of the pregnant and multiparous women in the control groups were within the same age brackets compared with the majority of women in the test groups of the primary infertile, secondary infertile and spontaneous aborter groups.

The etiology of reproductive failure has severally been implicated in the disturbance of thyroid homeostasis and attempt has been made to control it with the targeted treatment of the disease condition identified during investigations (Di-*Siomone, et al., 1999* ; Kessler et al., 2008).

The importance of thyroid hormones in metabolic regulation and control of reproduction cannot be over emphasized. A normal thyroid functioning system ie euthyroid tissue can still be subjected to stress due to derangement of immune system when auto antibodies are raised against self (auto) antigens. In the Euthyroid, the normal thyroid functioning and hormonal regulation still goes on, but the effective responses are truncated at another level, especially with immune interference (*El-Roeiy and Gleicher,1988;* Anatoly et al., 2010). It has been reported that Caucasians women with auto immune disease have an increased frequency of reproductive failure (*Coulam 1992*; Gleicher and Barad 2007).

Thyroid auto-antibodies have been predicted to be independent markers for pregnancies at risk for loss. The women who have significant anti-thyroid antibodies levels miscarry at approximately twice the rate of women who have no anti-thyroid antibodies, therefore history of two or more pregnancy losses or unexplained infertility should be investigated for the presence of anti-thyroid antibodies (*Hill and Chol,2000*; Ntrivalas et al., 2005).

This study agrees with previous reports (*Coulam 1992*; Coulam et al., 2006), which has shown that, high titers of this auto-thyroperoxidase in Euthyroid patients (i.e. without clinical evidence of thyroid dysfunction), is a positive phenomenon, in association with recurrent pregnancy loss. In this study the anti-Thyroglobulin (anti-TgAb) and anti-Thyroperoxidase (anti-TPOAb) auto antibodies mean titer levels showed that the anti-TgAb and anti-TPOAb were higher in test groups compared to the control groups, at $p < 0.05$. The anti-TgAb levels of the three tests group were significantly higher than the control groups. Whereas it was in only the secondary infertile women group was the anti-TgAb titer levels, significantly higher (at $p<0.05$) within the test group as shown in Table 2. The anti-TPOAb mean titer levels in secondary infertile, the spontaneous aborter and primary infertile women in this study were significantly higher compared with the control groups thus providing the primary marker for the reproductive failure.

The result obtained in Table 2 that showed positive anti-TPO-Ab titer mean levels were in pregnant group, multiparous group and nulligravida group, that were significantly high within the control groups, this suggest that low levels of anti-Tg-Ab may not hinder re-productivity.

There are increasing number of observations of different immune cell populations that display changes in their number and/or activation status during progression of autoimmunity (Anatoly et al., 2010; Lee and Chiang 2012). Recent findings demonstrated that gender also can have a significant impact on immune cell homeostasis and function, leading to significant differences in immunity between animals of different genders, with female predominance in autoimmunity (Quintero et. al. 2012). Therefore, immunologic changes that happen in different genders with age might not only increase our understanding of sex- and age-related immune system alterations, but also can shed some light on phenomenon of female-biased autoimmunity.

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