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Thyroid autoantibodies in euthyroid women with recurrent abortions and infertility

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Abstract

Background: Evidences suggest an association between the prevalence of thyroid peroxidase (anti-TPO) and anti thyroglobulin (anti-Tg) with recurrent abortions and infertility. Iodine deficiency was once endemic in Iran and little data is available about the prevalence of these antibodies in different groups of fertile or infertile individuals.

Objective: This case control study was designed to compare the presence of anti-TPO and anti-Tg in four groups of women to reveal their role in the etiology of recurrent abortion and infertility.

Materials and Methods: Four groups of euthyroid women referring to Avicenna Infertility Clinic in Tehran were selected; 95 cases as fertile controls and 70, 78 and 137 cases with male and female factor infertility and recurrent abortion respectively. TSH, anti-TPO and anti-Tg were evaluated by chemiluminescent immunoassay.

Results: The prevalence of the above mentioned autoantibodies in euthyroid controls was about 25% and the percentage of people with an anti-Tg >500 was two times bigger in the abortion group compared to the control group ($p<0.05$) and the proportion of people with an anti-Tg >500 in younger cases in the abortion group was significantly higher than the rest of the cases ($p<0.05$). Anti-TPO distribution had no significant differences**.**

Conclusion: There were no statistically significant differences among four groups. It seems that more comprehensive studies are needed to reach a common conclusion about thyroid autoantibodies in women with recurrent abortions in different groups and different parts of Iran. In addition, dividing the recurrent abortion and infertility groups on the basis of their etiologies could be effective.

Key words*: Recurrent abortion, Infertility, Anti-thyroglobulin antibody, Anti thyroid peroxidase antibody, Eeuthyroid.*

Introduction

Traditionally, recurrent abortion has been defined as the occurrence of three or more clinically recognized pregnancy losses before 20 weeks from the last menstrual period. Using this definition, recurrent pregnancy loss occurs in approximately 1 in 300 pregnancies. Clinical investigation of pregnancy loss, however, is sometimes initiated after two consecutive spontaneous abortions, especially when fetal heart activity has been identified before pregnancy losses, when the women are older than 35 years of age, or when the couple has had difficulty conceiving (1).

In women with recurrent abortions the cause of pregnancy termination remains unknown in

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approximately 50% of the cases, despite extensive evaluations (2).

Infertility is defined as a failure to conceive after 12 months of unprotected intercourses. About 18–20% of couples in reproductive age are infertile (3). Recent studies in humans suggest that an unexplained reproductive failure can be influenced by some immunological abnormalities (4). There are different studies about influence of thyroid autoantibodies on recurrent miscarriages and infertility in euthyroid women since early 1990s. The overall conclusion that is reached from these data depicts that recurrent abortion is associated with an increased incidence of thyroid antibody positivity (5, 6). Goiter is endemic in Iran. Local studies in Iran in the 1980s and a large survey in 1989-1990 revealed that goiter prevalence was much higher than previously reported, as goiter rate was greater than 60% in the majority of provinces throughout Iran. Iranian Ministry of Health and Medical Education set up the Iranian National Committee for the control of Iodine Deficiency Disorders (IDD) in 1989. Production and distribution of iodized salt with 40 mg potassium iodide per kg of sodium chloride began and education of policy makers, health personnel, and the public started in 1990. However, a rapid survey revealed less than 50% of the population consumed iodized salt. Therefore, the first law on mandatory iodization of all salts for household use was passed in 1994. Further rapid surveys showed more than 90% of the households consumed iodized salt (7).

Autoimmune thyroid disorders are less prevalent in iodine deficient than in iodine sufficient regions. Iodine supplementation may increase the frequency of lymphoid infiltrates of the thyroid and serum thyroid antibody levels (8). As such studies had not been performed on Iranian patients; it was decided to compare anti thyroid antibodies in patients with impaired fertility to that of fertile women.

Materials and methods

We designed a case-control study then assayed serum levels of thyroid peroxidase (anti-TPO) and thyroglobulin (anti-Tg) antibodies in 380 euthyroid women attending Avicenna Infertility and Recurrent Abortion Clinic and its laboratory from September 2006 to February 2007. The cases were divided into four groups as control (fertile) women with at least one child (95 cases), male factor infertility (70 cases), female factor infertility (78 cases), and recurrent abortion groups with a history of two or more consecutive recurrent abortions (137 cases). All the participants signed a consent form, provided by the Avicenna Ethics Committee to participate in the trial. All serums were collected and tests were performed by single technician and same kits.

Thyroid stimulating hormone (TSH) was checked in all 380 cases before performing the assays and all were euthyroid without any history of thyroid diseases, thyroid drug intake or autoimmune diseases. Commercially available kits (DiaSorin Company, Italy) were used to measure serum concentrations of TSH, anti-TPO and anti-Tg using chemiluminescent immunoassay method by LIAISON analyzer (Germany).

The reference ranges for the mentioned hormones are as follows: TSH; 0.3-4.2 mIU/l, anti-TPO; 1-16 IU/ml and anti-Tg; 5-100 IU/ml. The statistical analysis was performed using SPSS software, version 11.5.

Statistical analysis

All values were expressed as mean±SD. Kolmogorov-Smirnov test was used to assess the normality of the data but no normality was seen either totally, or in the four groups, therefore, Chi-Squared, Mann-Whitney non-parametric U-test, Kruskal-Wallis tests, and multiple linear regression model were used as appropriate. P-values smaller than 0.05 were regarded as significant.

Results

The studied groups were 19-48 years old, with a mean age of 31.7±6.4 years and their TSH levels were 0.3-4.2 mIU/l, with a mean value of 2.03±0.94, all being in normal range. In the four studied groups, anti-Tg and anti-TPO measurements were as are shown in table I. The evaluations showed that the measurements of the two variables and their values for the four groups did not follow a normal distribution; therefore non-parametric testes were applied for data analysis.

Anti-Tg and anti-TPO values were compared in the four groups but no significant differences were seen, although positive anti-TPO and anti-Tg percentage were higher in the control group and the group with recurrent abortions respectively. Eliminating the interference caused by age distribution imbalances in the four groups, a linear multiple regression model was used and no significant differences were observed, even at the absence of the probable compounding effect of age. Two by two, comparison of the control and case groups showed no significant differences.

Anti-Tg values were divided into there subgroups of <100, 100-500 and >500. The lowest number of cases with an anti-Tg <100, were in the control group (75.8%) and the highest number of cases with an anti-Tg <100, were on the abortion group (85.4%), but the percentage of people with

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an anti-Tg >500 was two times bigger in the abortion group compared to the control group (8.8% vs. 4.2%) and the difference was statistically significant ($p<0.05$) (Table II).

However, dividing anti-TPO values to three subgroups of <16, 16-100 and >100 showed no significant statistical differences among the four studied groups. The proportion of cases in the control group with an anti-TPO of >100 was more than the rest of the cases.

Regarding the probable confounding effect of age on the findings, the studied cases were divided into three age groups of <30, 31-40 and >40 years. Anti-TPO and anti-Tg were compared in the four groups regarding the mentioned age groups. It was known that anti-TPO distribution had no significant differences but the proportion of people with an anti-Tg >500 in younger cases in the abortion group was significantly higher than the rest of the cases (10.6%, $p<0.05$).

Out of 138 patients in recurrent abortion group, 77 individuals had 3 or more abortions but there were not significant difference between these subjects and the control group. Number of children had no significant effect on the autoantibodies in the control group.

Table I. Anti-Tg and Anti-TPO in the four study groups.

Groups	Number	Age (year)	Anti –Tg		Anti-TPO	
			Median	% of positive*	Median	% of positive**
Controls	95	20-48	17.5	24.2	2.6	25.3
Male factor infertility	70	20-43	16.7	22.9	2.6	20
Female factor infertility	78	19-47	17.3	16.6	2.8	12.8
Recurrent abortion	137	19-45	14.4	14.6	3.7	19

*>100 IU/ml **>16 IU/ml

Table II. Anti-Tg titers in the four studied groups.

Groups	Anti-Tg levels			
	Less than 100 Number (%)	100-500 Number (%)	More than 500 Number (%)	Total Number (%)
Controls	72 (75.8)	19 (20)	4 (4.2)	95 (100)
Male infertility	54 (77.1)	14 (20)	2 (2.9)	70 (100)
Female infertility	65 (83.3)	10 (12.7)	3 (3.8)	78 (100)
Recurrent abortion	117 (85.4)	8 (5.8)	12 (8.8)	137 (100)
Total	308 (81.0)	51 (13.4)	21 (5.5)	380 (100)

Discussion

The state of iodine-deficiency and high prevalence of goiter and hypothyroidism in Iran, iodine supplement therapy began in mid 1990s but lack of adequate information on the state of thyroidal autoantibodies and their role in recurrent abortions and infertility, encouraged us to undertake this study. Regarding other studies carried out in other countries (5, 9-11) we expected higher prevalence of these autoantibodies in recurrent abortion and female infertility. Azizi *et al* in Shiraz (1981) showed a low prevalence of thyroid autoantibodies (2% among healthy volunteers and 3% among goitrous individuals) during a period of iodine deficiency in Iran (12). A somewhat similar prevalence of anti-TPO and anti-Tg was detected in adult populations in Tehran, Iran during a 1983-1984 study by the same authors. Nonetheless, thyroid antibodies were measured by agglutination method in both the above-mentioned studies (7). The frequency of autoantibody association with hemagglutination (HA) differs greatly from one study to another, depending on the way patients are recruited, the tests performed and the observed threshold values (13). Unavailability of sera restricted them in re-measurement of antibody levels by IEMA method, which was used for antibody measurement during the years 1999-2000. The prevalence of positive anti-TPO and anti-Tg were 12.5 and 16.8% in adult populations of Tehran during 1999-2000 (i.e., 5 years after national salt iodization). Although statistical measurements of the prevalence of antibodies between 1983-1984 vs. 1999-2000 is not possible, the large differences lie in the prevalence of anti-TPO (from 3.2 to 12.5%) and anti-Tg (from 4 to 16.8%) which can not simply be overlooked because of differences in measurement methods. It seems that salt iodization resulted in a modest increase in both anti-TPO and anti-Tg level

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in adult population but it was not accompanied by an increase in thyroid function abnormalities (7). In another study done in Isfahan, another iodine-deficient area in Iran, by Aminorroaya *et al* recently, 26.7% of euthyroid women had anti-TPO and 19.8% had anti-Tg (14). In studies in other countries, increases in autoantibody titers have been seen upon iodine supplement therapy and autoimmune thyroiditis prevalence showed a threefold increase after seven years (15). Therefore, researchers emphasize that iodine supplementation should be done only in iodine-deficient areas with close observation (16). Despite our preliminary hypothesis, the findings indicated no significant differences among the four studied groups, although the prevalence of auto-antibodies in the euthyroid fertile group was close to that of Aminorroaya's results (25.2% anti-TPO, 24.2% anti-Tg and 26.7%, 19.8% respectively). High prevalence of anti-TPO was seen in the control group while anti-Tg was more prevalent and with higher titers in the abortion group. As our study was performed in a referral center in Tehran, we had patients from different areas with various nutritional stati and this fact could have affected the results. Another point to be regarded was selection of fertile women as controls which in some way might have affected the results, as these autoantibodies are more prevalent in them (17, 18) although in most studies the controls are selected among them.

Conclusion

In spite of our expectation there were no statistically significant differences between the four groups.

Regarding the varied consumption of iodine-rich diets in Iran, lack of data from different areas and different groups, and various methods of autoantibody detection, all made it somehow challenging to reach a common conclusion. Therefore, more comprehensive studies with controlled iodine intake checks (urinary tests, for example) and larger populations are suggested. In addition dividing the recurrent abortion and infertility groups on the basis of their etiologies could be effective; especially subgroups with immunological factors or unknown causes of recurrent abortions and infertility should be particularly assessed.

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