

# Prevalence of antithyroid antibodies in patients with unexplained infertility

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## Abstract

**Objective:** To evaluate the relative prevalence of antithyroid antibodies in unexplained infertility compared to other types of infertility.

**Patients and methods:** The study comprised of 96 subfertile couples and 80 parous women attending outpatient clinic in Mansoura University Hospital. There were 30 patients had tubal causes, 16 patients had PCOS, 10 patients had endometriosis and 40 had unexplained infertility. Antithyroid auto-antibodies (antithyroglobulin and antimicrosomal) were estimated in the sera of all patients.

**Results:** There were no significant differences in the frequency of antimicrosomal antibodies and antithyroglobulin in subfertile cases compared to the controls (25% and 22% versus 12% and 10%, P value 0.22 and 0.12, respectively). Subgroup analysis had revealed significantly higher frequency of women with positive antimicrosomal and antithyroglobulin antibodies in couples with unexplained infertility compared to fertile controls.

**Conclusion:** A significantly higher proportion of thyroid auto-antibodies existed in women with unexplained subfertility compared to the fertile women.

**Key words:** Subfertility, thyroid antibodies, unexplained infertility

## Introduction

Unexplained infertility is defined as failure to conceive after at least one year of continuous unprotected sexual intercourse in which the standard infertility testing revealed no cause for this failure. The prevalence of unexplained subfertility was estimated to be approximately 10-20 % of all cases of infertility (1). The reason for unexplained infertility is enigmatic and several hypothetical causes, however, had been described. Abnormalities in gametes, implantation failure, hostile cervical mucus and autoimmune disorders were all suggested to play a role (2-4).

Autoimmunity has been linked to several reproductive conditions including premature ovarian failure, unexplained infertility and recurrent pregnancy loss (2, 4-6). Antithyroid antibodies had not been infrequently isolated from women with subfertility (7, 8). A number of antithyroid antibodies have been isolated from women with thyroid dysfunction (9). Thyroid peroxidase (Tpo) is a glycoid protein present on the thyroid cell surface. It is responsible for the iodination of tyrosine residues on thyroglobulin (TG) as well as the intramolecular coupling reaction of iodinated tyrosine leading to the formation of thyroxine and triiodothyronine (10, 11). Antithyroglobulin antibodies (ATA) and antithyroid peroxidase antibodies (microsomal antibodies or AMA) had been isolated from women with unexplained infertility as well as women with premature ovarian failure (12).

NICE guidelines for subfertility management do not recommend screening for thyroid dysfunction in a rather asymptomatic subfertile woman. Neither do they recommend screening for autoimmunity in unexplained subfertility (<http://www.NICE.com>). Nevertheless, these recommendations based on limited number of studies investigating the associations between antithyroid antibodies and unexplained infertility. Hence, we decided to perform this case-control study to assess the prevalence of thyroid antibodies in subfertile women and evaluate the relative prevalence of thyroid antibodies in unexplained infertility compared to other types of infertility.

## Patients and Methods

The study comprised of 96 subfertile couples among those attending Mansoura University Hospital outpatient clinic and a private practice setting during the period from September 2006 till September 2010. Eighty parous women, matched for age, were recruited as a control group. The protocol of this study was approved by the local ethical committee of the institution and all participants gave an informed consent before inclusion in the study. Women aged 40 years or more, women with past or current history of endocrine or autoimmune disease and women with history of recurrent miscarriage were excluded from the study. All patients included in the study were subjected to hysterosalpingography for tubal patency, midluteal serum progesterone for confirming ovulation, laparoscopy and semen analysis for their partners. There were 30 patients had tubal causes, 16 patients had PCOS, 10 patients had endometriosis and 40 patients were diagnosed to have unexplained infertility. Unexplained infertility was defined as inability to conceive for 1 year or more whenever normal semen analysis, positive ovulation (mid-luteal phase progesterone), and

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patency of both fallopian tubes was documented. Aged-matched control group comprised of 80 women below 40 years old and had at least one living baby. Women in the control group were excluded if they had experienced any previous difficulty in conceiving for one year or more, past or current history of endocrine or autoimmune disease or history of recurrent miscarriage.

Hormonal assay for FSH, LH, TSH, T3, T4 was done using electrochemiluminescent immunoassay technique according to the method of Beastall et al (1987), while prolactin was determined according to the method of Fahie–Wilson and Soule (1997) (13, 14). Antithyroid autoantibodies (antithyroglobulin and antimicrosomal) were estimated in all patients by the indirect fluorescent (IFA) technique. The reaction occurs in two steps. The first is the interaction of thyroid antibodies in patient's sera with thyroid substrate. The second is the interaction of FITC labeled anti human immunoglobulin with thyroid antibodies attached to the thyroid tissue producing apple – green staining in a positive assay (15).

### Statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Science version 16.0 (SPSS Inc., Chicago, IL, USA). Data were checked for normality in distribution and using Student t test (t), chi-square test ( $\chi^2$ ), Mann-Whitney (U) test where appropriate. When a quantitative analysis of the data was performed, groups were compared by analysis of variance with Scheffé's post hoc analysis. Significance was defined as  $P \leq 0.05$ .

### Results

Data regarding differences in the demographic and basal line features between both infertile group (cases) and fertile one (control) are presented in Table 1. The mean age, height, weight, BMI, serum basal FSH and LH values did not differ significantly between the two groups. The median serum TSH level was significantly higher in the subfertile group compared to the controls.

The percentages of individuals positive for antimicrosomal antibodies and antithyroglobulin antibodies are shown in Table 2. There were no significant differences in the frequencies of antimicrosomal antibodies and antithyroglobulin in subfertile cases compared to the controls (25% and 22% versus 12% and 10%, p value 0.22 and 0.12, respectively). Subgroup analysis had revealed significantly higher frequencies of women with positive antimicrosomal and antithyroglobulin antibodies in couples with unexplained infertility compared to fertile controls (Table 3).

### Discussion

In this study, there were higher proportions of positive thyroglobulin and micriosomal autoantibodies in infertile group although the difference was not statistically significant when compared with the control group.

The results of this study point out to an association between unexplained subfertility and the presence of anti-thyroid antibodies. It remains to be determined whether these antibodies might have played a role in the low reproductive performance of these couples or not. Two plausible hypotheses had been suggested for the presence of these antibodies; a phenomenon accompanying immune system activation by specific autoantigens or by immune activation initiated by viral and bacterial inflammation.

Our results were in agreement with Poppe et al (2003) who reported a higher proportion of positive antibodies in sera of

women of couples diagnosed with subfertility compared with fertile controls, however, the difference has yet to reach the statistical level of significance(9). Moreover, Abalovich et al (2007), reported no significant difference of thyroid autoantibodies between a group of infertile patients and a control group (16). This is in contrast to Grassi et al (2001) who found a high prevalence of thyroid autoantibodies in infertile patients (17). Nevertheless, the significantly higher prevalence of thyroid autoantibodies in women with an overall poor reproductive performance was highlighted in more studies though the exact mechanism of action remains unknown (18, 19).

In our series, there were a higher proportion of thyroid antibodies in women with unexplained subfertility. This finding supports similar findings by other researchers (8, 20), however, it remains difficult to recommend any change in current management, whether screening or treatment, of idiopathic infertility based on our findings. The small sample size in our study as well as the nature of our study as a case control study may render it prone to some methodological outflows. Moreover, there is almost no evidence that the use of any specific treatment, as immune modulator for example, could improve the prognosis. Nevertheless, based on the relatively big difference (effect size) in the proportion of these antibodies in women with unexplained infertility compared to fertile women, we do recommend more research in this area.

To conclude, our study has shown no difference in the proportion of antithyroglobulin antibodies and antimicrosomal antibodies in the sera of subfertile women compared to fertile controls. However, subgroup analysis has revealed a significantly higher proportion of these antibodies in women with unexplained subfertility compared to the controls. The implications of our finding on clinical practice remain unclear and more research is warranted.

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**Table 1:** comparison between subfertile women and parous women as regard age, BMI, TSH level, LH level, FSH level

groups	Subfertile women (cases) n=96	Parous women (controls) n=80	P value
Age ( years)	24 ± 3	26 ± 4	0.8
Body mass index(BMI) Mean±SD	23.5 ± 0.5	24. 3 ±0.6	0.4
TSH ( MIU \ ML ) Median [interquartile range]	7.23±1.1	1.87±0.4	0.02
LH ( IU/L) Mean±SD	21 ± 0.5	21 ± 0.7	0.8
FSH ( IU/L) Mean±SD	5.3 ± 0.2	5.1 ± 0.7	0.7

**Table 2:** Thyroid antibodies in infertile patients and control group

Groups	Group A n = 96	Group B n = 80	P value
Number and percentage of cases with positive antimicrobial antibodies	30 ( 25 % )	12 ( 15% )	0. 22
number and percentage of cases with positive antithyroglobulin antibodies	26 (22%)	8 ( 10 % )	0. 12

**Table 3:** Thyroid antibodies in unexplained infertility patients and in the control group

Groups	Unexplained infertility patients n =40	Control group n = 80	P value
Antimicrobial antibodies number and percentage of positive cases	18 ( 50 % )	12 ( 15 % )	0.005*
antithyroglobulin number and percentage of positive cases	14( 38.88 % )	8 ( 10 % )	0.009*