Thyroid disorders in infertile women

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INTRODUCTION

Infertility is defined as the inability to conceive after one year of regular intercourse without contraception. The prevalence of infertility is estimated between 12 and 14% and remains stable in recent years [1, 2]. It thus represents a common condition, with important medical, economic and psychological implications. According to a standard protocol infertility evaluation usually identifies different causes, including, male infertility (30%), female infertility (35%), the combination of both (20%), and finally unexplained or “idiopathic” infertility (15%) [3]. Female causes of infertility comprise endometriosis, tubal damage and ovulatory dysfunction (OD).

Recently, it has been suggested that infertility may be caused by the presence of auto antibodies, among them thyroid immunity has been incriminated.

Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy and to adversely affect pregnancy outcome [4]. Positive thyroid antibodies even in the presence of euthyroidism increase the risk of miscarriage, by a factor 2 to 3 [5]. Data on the relationship between thyroid disorders and infertility remain scarce and the association with a particular cause of infertility has not thoroughly been analyzed [6, 7]. We therefore performed this case-control study to determine the rela-
fertility? and 3) do these antibodies influence outcome of the in vitro fertilization procedure?

The answers to the two first questions were evaluated with a case-control study looking at the occurrence of thyroid autoimmunity and thyroid function tests among women of infertile couples (n=438), presenting for the first time at the department of reproductive medicine. For comparison, a control population of parous women (n=100), matched for age, was included.

In 45% of the infertile couples a female cause of infertility was identified: endometriosis (11%), tubal disease (30%) and ovarian dysfunction (59%). Male infertility was diagnosed in 38% and idiopathic infertility in 17% of the couples.

Mean serum TSH levels were significantly higher in patients with infertility compared with control patients: 1.6 ± 2.6 versus 1.2 ± 0.7 mIU/L. The proportion of positive TPO-Abs was higher in all women of infertile couples, compared with controls (14% versus 8%), but the difference was not significant. Considering only the female causes of infertility a significant higher proportion of women had positive TPO-Abs compared with controls (18% versus 8%), and in particular a high prevalence of thyroid autoimmunity was found in women suffering from endometriosis (29%).

Both hypo- and hyperthyroidism were more frequent when TPO-Abs were positive, compared to women without thyroid autoimmunity.

The results of the present study indicate that endometriosis, increases the relative risk for associated thyroid autoimmunity to 2.3, and therefore screening for thyroid auto-antibodies could be systematically proposed in these women.

Key words: Thyroid, female infertility.

PATIENTS AND METHODS

438 consecutive women, aged 21-50 years (mean 32 ± 5 years) consulted at the Center for Reproductive Medicine, between October 1999 and November 2000. All women were systematically screened on the third day of their menstrual cycle (when present) for the presence of thyroid peroxidase antibodies (TPO-Abs), serum thyrotropin (TSH) and free thyroxine (FT4). The standard infertility workup included medical history, gynecological examination, transvaginal ultrasonography, hormonal profile, screening for infectious disease and whenever indicated hystero-salpingography and/or laparoscopy. Female causes of infertility were defined, according to WHO criteria: endometriosis (except stage I) [8], tubal damage or OD [9]. Male infertility was identified when the semen was abnormal and no female cause was present. In the case of a normal sperm analysis and the absence of a female cause of infertility, the couple was considered to have idiopathic infertility.

One hundred randomly selected, age-matched parous women with a mean age of 33 ± 4 years, and no history of reproductive problems, were screened for the same thyroid parameters and served as controls.

Serum TSH and FT4 were measured using a third generation electro-chemiluminescence immunoassay (Roche; Mannheim; Germany). Reference values: 0.27-4.2 mIU/L for TSH and 9.3-18.0 ng/L for FT4.

Thyroid peroxidase antibodies (TPO-Abs) were determined using a RIA-kit (B.R.A.H.M.S. Diagnostica; Berlin; Germany). Reference value: 0-100 kU/L. TPO-Abs titer were considered positive when titers exceeded 100 kU/L.

Statistical analyses was performed using SPSS-program, by means of a $\chi^2$ test (Fisher’s exact). Correlations between variables were assessed using Spearman’s test, and differences between mean values by the Mann-Whitney-U test. All statistical tests were considered statistically significant whenever $P < 0.05$.

RESULTS

Infertility causes

The characteristics of the women of infertile couples are presented in table I.

No differences were noted in age, between women of infertile couples and the control population.

Male infertility represented 38% of the infertility problem and “idiopathic” infertility was diagnosed in 17%. In the other 45% the reason of infertility was of female origin. In this female cause group, endometriosis represented 11%, tubal disease 30% and OD 59% (table II). The age of women of couples with male infertility was slightly lower, compared to controls (31 ± 5 yrs versus 33 ± 4 yrs; p <0.05) (table I).

Thyroid autoimmunity

In the study group, positive TPO-Abs (table I) were documented in 14% of women; whereas in the control group they were present at a rate of 8%, the difference between the two groups being statistically non signifi-
significant (p = 0.31). With respect to the prevalence of TPO Abs in the female subgroup of the study population, such antibodies were found in 18% and this was statistically higher than in the control group (p = 0.024). Women with endometriosis represented the subgroup with the highest increased prevalence of positive TPO-Abs, compared with the controls: 29% versus 8% (p = 0.016) (Table II).

The proportion of women of couples with a male origin of infertility or idiopathic infertility and positive TPO-Abs were comparable to the proportion positive in the control population (11 and 7% resp.).

**Thyroid function**

In all study patients, mean serum TSH was slightly higher, compared with the control patients (1.6 ± 2.6 mIU/L versus 1.2 ± 0.7 mIU/L; p = 0.006). Women with female infertility (1.7 ± 3.8 mIU/L), and particularly patients with O.D. (1.9 ± 4.9 mIU/L) had higher mean basal TSH in comparison to control patients (resp. p = 0.05 and p = 0.003).

On the other hand, mean serum TSH values were also found to be more elevated in the group of patients with idiopathic (1.5 ± 0.9 mIU/L) and male infertility (1.4 ± 0.7 mIU/L).

The prevalence of alterations of thyroid function, as defined by a suppressed or increased basal TSH value, was comparable in the study population and control subjects (data not shown).

Concerning FT4, there was no difference among the groups (Table I).

Figure 1 shows mean TPO-Abs titer as a function of serum TSH. Infertile women with a normal TSH were arbi-

<table>
<thead>
<tr>
<th>Infertility causes</th>
<th>Age*</th>
<th>TSH °</th>
<th>FT4*</th>
<th>aTPO*</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (n = 197) 45%</td>
<td>34 ± 6</td>
<td>1.7 ± 3.8*</td>
<td>12 ± 3</td>
<td>18%*</td>
<td>2.25</td>
<td>1.02-5.12</td>
</tr>
<tr>
<td>Male (n = 168) 38%</td>
<td>31 ± 5*</td>
<td>1.4 ± 0.7*</td>
<td>12 ± 1</td>
<td>11%</td>
<td>1.32</td>
<td>0.55-3.17</td>
</tr>
<tr>
<td>Idiopathic (n = 73) 17%</td>
<td>32 ± 5</td>
<td>1.5 ± 0.9*</td>
<td>12 ± 2</td>
<td>7%</td>
<td>0.86</td>
<td>0.27-2.73</td>
</tr>
<tr>
<td>All patients (n = 438) 100%</td>
<td>32 ± 5</td>
<td>1.6 ± 2.6*</td>
<td>12 ± 3</td>
<td>14%</td>
<td>1.68</td>
<td>0.78-3.65</td>
</tr>
<tr>
<td>Controls (n = 100)</td>
<td>33 ± 4</td>
<td>1.2 ± 0.7</td>
<td>12 ± 2</td>
<td>8%</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

° results expressed as mean ± SD  
°% of patients with a-TPO >100 kU/L  
RR = Relative Risk; CI = Confidence Interval  
p < 0.05 vs controls

<table>
<thead>
<tr>
<th>Female causes</th>
<th>TSH °</th>
<th>aTPO*</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis (n = 21) 11%</td>
<td>1.4 ± 0.8</td>
<td>29%*</td>
<td>3.57</td>
<td>1.09-11.8</td>
</tr>
<tr>
<td>Tubal (n = 60) 30%</td>
<td>1.5 ± 1.4</td>
<td>18%</td>
<td>2.29</td>
<td>0.86-6.07</td>
</tr>
<tr>
<td>OD (n = 116) 59%</td>
<td>1.9 ± 4.9*</td>
<td>16%</td>
<td>2.05</td>
<td>0.85-4.91</td>
</tr>
</tbody>
</table>
| Controls (n = 100) | 1.2 ± 0.7 | 8% | / | /

° results expressed as mean ± SD  
°% of patients with a-TPO >100 kU/L  
RR = Relative Risk; CI = Confidence Interval  
p < 0.05 vs controls

trarily subdivided into two categories, women with a low normal serum TSH (between 0.27-2.5 mIU/L) and a high normal TSH (2.5-4.2 mIU/L). A significantly higher rate of high normal TSH was present in women with thyroid autoimmunity, compared with patients negative for thyroid antibodies, and this considering all types of infertility. TSH correlated significantly with TPO-Abs titer present at the initial evaluation. Women with high normal TSH (>2.5mU/l), had higher levels of TPO-Abs, compared to women with low normal TSH. All patients with increased TSH (> 4.2 mU/L) exhibited significantly increased levels of TPO-Abs, compared to patients with normal TSH.

Relative risk of associated thyroid autoimmunity
For all female patients of couples with infertility taken together, the RR of associated thyroid autoimmunity is slightly, but not significantly increased: 1.68 (95% CI: 0.78-3.65). However, in case of female origin, the woman has an increased risk of positive TPO-Abs of 2.25 (95% CI: 1.02-5.12), p =0.045, and this risk further increases in the presence of endometriosis to 3.57 (95% CI: 1.09-11.8), p =0.036. Finally, in idiopathic and male infertility, the women of these couples have no statistically significant associated risk of being positive for TPO-Abs (see table I).

DISCUSSION
The clinical relevance of autoimmunity in infertility is still controversial [10]. Several studies have investigated the possible association between infertility and thyroid autoantibodies in the infertility practice. Risk of infertility associated with thyroid autoimmunity is summarized in table III. The causes of infertility, the characteristics of the control population used and the types of antibodies (thyroglobulin, microsomes, TPO) tested differed from study to study and could explain heterogeneity among them as well as contradictory results obtained.

When studies examined the association between antibodies and a particular cause of infertility, biases related to other aspects of the disease examined may have been introduced. On the other hand, several authors agreed on an increased prevalence of spontaneous abortion in apparently euthyroid women who had thyroid antibodies [5]. The ultimate goal of the fertility treatment is to achieve pregnancy. It is thus of interest to define whether a particular cause of infertility predisposes to thyroid autoimmunity and to assess thyroid function and outcome of treatment, not only in terms of pregnancy rate, but also in terms of life birth.

The aim of the present study was firstly to evaluate the prevalence of thyroid antibodies in women with reproductive failure compared to a control group and secondly to investigate the possible association between these antibodies and the different causes of infertility.

The study reveals that women with a female cause of infertility have a higher prevalence of positive TPO-Abs and among them women with endometriosis have a significantly higher prevalence compared with controls. Gerhard et al reported similar results in endometriosis [11]. The association between thyroid autoimmunity and endometriosis, strengthens the hypothesis of an al-
tered immunity in this disease. Numerous types of non-organ specific antibodies were found in association with endometriosis [10] as well as a deficient cellular immunity. Natural killer cell activity is reduced, in association with an increased concentration of leukocytes and macrophages in the peritoneum of patients with this disease [12, 13]. The immune system may thus determine who will develop endometriosis. Consistent with these previous assessments the higher prevalence of positive TPO-Abs in the present study screening for thyroid autoimmunity in women suffering from endometriosis is indicated.

As shown in table I, the proportion of patients with thyroid autoimmunity was also increased, although not significantly, in other causes of female infertility (tubal, OD). A more generalized immune dysfunction in these pathologies remains speculative, although disturbed immunity and especially thyroid dysfunction could interfere with genital tract physiology.

The relationship of infertility with thyroid dysfunction was overlooked in a retrospective study in 299 infertile women showing an overall prevalence of hypothyroidism (both subclinical and overt) of 4% [14]. In this study, subgroup analysis identified 6% of hypothyroid women among those with OD, 2.6% among those with tubal infertility, 0% among those with endometriosis, 1.5% in male infertility and 5% among women with idiopathic infertility. In two other prospective studies, increased serum TSH was identified in 0.7% and 2.3% respectively of women with infertility, the majority of them presenting infertility due to OD. However, these two studies did not include a control group of healthy fertile women [15, 16]. The clinical implication of overt thyroid dysfunction in infertile women is explained by the direct effects of thyroid hormones on granulosa and luteal cells, and on oocytes [15, 17]; hence suggesting an interference with normal ovarian function. In case of overt thyroid dysfunction, treatment should be instituted as a primary therapeutically act.

In the present work, the overall mean serum TSH was significantly higher in the women of infertile couples than in the controls and in particular in women of the OD subgroup. In spite of the overall mean higher TSH, only 1% of these women actually presented supranormal TSH values, except for women with tubal infertility with a prevalence of 3% of increased TSH (ns). The low prevalence of overt thyroid dysfunction does not allow speculations on thyroid dysfunction and associated infertility in the tubal and OD subgroup.

The higher prevalence of positive TPO-Abs in all study- and control patients with abnormal TSH in all groups examined only confirms the frequent autoimmune origin of thyroid dysfunction in this young female population.

In the female cause of infertility, we documented a higher prevalence and a higher level of TPO-Abs in patients with a high normal TSH value, compared to patients with a low normal TSH value. In these subgroups, arbitrarily defined on the basis of basal TSH values, free T4 concentrations were similar (data not shown). We propose that because these women have a higher setting of their TSH setpoint, they may represent a potential target group for intervention trials, considering the possibility of minimal tissue hypothyroidism. Minute decrements in hormone synthesis may over time lead to

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>RM #</th>
<th>Sample size</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al [23]</td>
<td>1975</td>
<td>1</td>
<td>77</td>
<td>0.71</td>
<td>(0.30, 1.72)</td>
<td>0.44</td>
</tr>
<tr>
<td>Roussev et al [6]</td>
<td>1996</td>
<td>2</td>
<td>45</td>
<td>3.00</td>
<td>(0.34, 25.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Geva et al [7]</td>
<td>1997</td>
<td>4</td>
<td>80</td>
<td>3.75</td>
<td>(0.81, 17.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Kutteh et al [24]</td>
<td>1999</td>
<td>3</td>
<td>688</td>
<td>1.32</td>
<td>(0.85, 2.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>Average risk</td>
<td></td>
<td></td>
<td></td>
<td>1.28</td>
<td>(0.88, 1.87)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Homogeneity
Chi square4.257
df3.000
P value0.235

Heterogeneity
Small sample size
Different control populations
Different methods used to measured anti-thyroid Abs
biochemical and functional signs ultimately affecting normal genital tract physiology [18, 20].

Recently, an intervention trial in women with recurrent abortions, positive TPO-Abs and mild thyroid dysfunction showed that the early administration of thyroid hormones allowed to significantly increase the number of live births, in comparison with the administration of intravenous immunoglobulin during pregnancy [21]. Although some criticism have been made in regard to the methodology of this study [22], it points to the fact that supplementing a relative thyroid hormone deficiency state favorably affects outcome of pregnancy.

Therefore, it remains important to delineate prospectively the impact of autoimmunity on thyroid function, during IVF and subsequent pregnancy, before treatment is envisaged.

In conclusion, the present study showed that the relative risk to have positive TPO-Abs in infertility due to a female cause and in particular related to endometriosis was significantly increased. Thyroid dysfunction itself is a condition interfering with normal ovarian function and was more frequent in women with positive TPO-Abs.

We therefore propose that a systematic screening of TSH, free T4 and TPO-Abs could be considered in all women with a female cause of infertility and especially in the case of endometriosis.

REFERENCES