Prospective pregnancy outcome in untreated recurrent miscarriers with thyroid autoantibodies


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The purpose of this study was to determine the prevalence of thyroid antibodies in women with recurrent miscarriage and to observe whether their presence was predictive of future pregnancy outcome. A total of 870 consecutive, non-pregnant women with a history of three or more pregnancy losses and normal parental karyotypes were investigated for the presence of thyroglobulin antibodies (TgAb) and for thyroid microsomal antibodies (TmAb). Thyroid antibodies were found in 162 (19%) women. TgAb only were found in eight women (5%); TmAb only in 98 (60%) and both TgAb and TmAb were found in 56 (35%). Thirteen women had a history of thyroid disease and a further 15 women were found to have abnormal thyroid function. All 28 were excluded from the pregnancy outcome study. Among the remaining 134 thyroid antibody positive women, 36 women were not tested and normal thyroid stimulating hormone results were obtained for 98. In the group proven euthyroid, 14 of 24 untreated pregnancies resulted in live births (58%). Among the 710 thyroid antibody negative women, 47 of 81 untreated pregnancies resulted in live births (58%). The future risk of pregnancy loss in women with unexplained recurrent miscarriage is not affected by their thyroid antibody status.

Key words: pregnancy/recurrent miscarriage/thyroid antibodies

Introduction

Thyroid antibodies have been shown to predict a greatly increased risk of miscarriage in the normal, euthyroid, antenatal population (Stagnaro-Green et al., 1990; Lejeune et al., 1993). Compared to the general antenatal population, thyroid antibodies are detected more frequently among women with a history of recurrent miscarriage (Edelman et al., 1986; Bussen and Steck, 1995; Kutteh et al., 1999). When found in women with unexplained or mechanical infertility, they have been reported to predict a low pregnancy rate per cycle of IVF (Geva et al., 1996; Bussen et al., 2000), and a high rate of subsequent miscarriage (Kim et al., 1998).

There are data suggesting an association between reproductive failure and abnormal autoimmune function, most notably when marked by the presence of antiphospholipid antibodies (Gleichert et al., 1993). Small studies have suggested that the presence of thyroid antibodies does not correlate with the presence of antiphospholipid antibodies, but appears to be an independent predictor of poor reproductive outcome (Pratt et al., 1993a; Bussen and Steck, 1997).

Although thyroglobulin antibodies (TgAb) are recognized markers of autoimmune thyroid disease, they lack a defined biological action (Braveman and Utiger, 1996). Thyroid microsomal antibodies (TmAb) are found in the serum of almost all patients with Hashimoto’s thyroiditis, in more than 70% of those with Grave’s disease, and, to a variable degree, in patients with non-thyroid autoimmune diseases and some normal subjects. Their titres do not correlate with thyroid functional status and do not necessarily fall with therapy. Thus, TmAb are also established markers of autoimmune thyroid disease, and again, their pathogenic role is not clearly defined.

The purpose of this study was to determine the prevalence of thyroid antibodies in women with recurrent miscarriage and identify any correlation with the presence of antiphospholipid antibodies. Those women who had no treatment during a subsequent pregnancy were studied to determine whether the presence of thyroid autoantibodies had a predictive value for future pregnancy outcome.

Materials and methods

All women attending St Mary’s Hospital Recurrent Miscarriage Clinic between January 1995 and September 1998 were investigated according to national guidelines [Royal College of Obstetricians and Gynaecologists (RCOG), 1998]. These comprised peripheral blood karyotyping of both partners, pelvic ultrasound scan, a hormonal profile, and screening for antiphospholipid antibodies. Couples with an abnormal karyotype were excluded from the study group. Hysterosalpingogram and/or hysteroscopy were performed only for those women with an abnormal ultrasound result or an additional history of delay in conception.

A total of 870 consecutive, non-pregnant women (median age 34, range 19–46) with a history of three or more consecutive miscarriages (median 4, range 3–12), not including ectopic pregnancies, was investigated for the presence of TgAb using Japanese Serodia ATG particle agglutination kits, and for TmAb antibodies using Serodia ATM. Pregnancies fathered by more than one partner were not excluded since the factors examined in this study were considered to be purely maternal. The principle of the test was to identify TgAb and TmAb by using indirect particle agglutination. Specimens of patient serum were tested using commercially made kits manufactured by Fujirebio Inc., Tokyo, Japan. These had been distributed by Mast Group Ltd, Bootle, UK. The method, in brief, was to add increasingly diluted serum samples to 10 IU wells on a microtitre plate. Sensitized
particles were added to each well, and unsensitized particles were added to an additional serum sample of the lowest dilution. The plates were incubated overnight at room temperature. Agglutination patterns of unsensitized particles and negative titres formed button-shaped patterns as the particles concentrated in the centre of the well. Positive titres showed a film of agglutinated particles substantially larger than the button in the negative wells. A test sample which showed a negative result with unsensitized particles and showed agglutination with sensitized particles at a dilution $\geq 1:100$ was interpreted as positive and reported as a titre (the highest dilution to give a positive well). A titre $>1:100$ for TgAb was considered positive, as was a titre $>1:400$ for TmAb. Those women positive for either or both TgAb and TmAb had their thyroid stimulating hormone (TSH) concentration determined using a monoclonal antibody, magnetic separation ‘sandwich’ assay, run on a Bayer Immuno 1 machine (Bayer Corp., Tarrytown, NY, USA). The minimum detectable concentration of TSH was 0.03 mIU/l, to a maximum of 150 mIU/l, beyond which dilution of the sample was required. Cross-reactivity of $<0.1\%$ was found with HCG, LH and FSH. Fifteen women with results outside the range 0.5–5.0 mIU/l were considered to have abnormal thyroid function and were further tested for total thyroxine using a latex agglutination automated immunoassay (also run on the Bayer Immuno 1 machine), and referred to an endocrinologist. Fourteen women with a history of treated thyroid disorder were excluded from the prospective pregnancy outcome study group, even if their TSH was within the normal range.

Sample collection and processing for the detection of the lupus anticoagulant was made in accordance with guidelines issued by the British Society for Haematology (Haemostasis and Thrombosis Taskforce, 1991). The dilute Russell’s viper venom time (dRVVT) was used together with a platelet neutralization procedure, and a dRVVT test ratio of $>1.1$ which corrected by at least 10% was considered positive. Both the immunoglobulin (Ig)G and IgM classes of anticardiolipin antibody (ACA) were assayed using a standard enzyme-linked immunosorbent assay (Loizou et al., 1985). An IgG ACA value of $>5$ IgG anticardiolipin (GPL) units and an IgM ACA value of $>3$ IgM anticardiolipin (MPL) units were considered positive (Khamashta and Hughes, 1993). All women with a positive test for antiphospholipid antibodies were restested at least 8 weeks after the initial positive test. Only women with persistently positive tests were considered to have antiphospholipid syndrome (Harris, 1987).

Once each woman had completed her investigations, the first conception she reported was followed prospectively. Enrolment began in January 1995 and ended on September 30, 1998. Ongoing pregnancies with a last menstrual period prior to this date were followed to their conclusion, the last delivery thus occurring in June 1999. The negative groups within the whole study population or within the pregnancy outcome study group, even if their TSH 149. Regrettably, no serum taken prior to pregnancy was available in 36 cases. TSH concentrations were performed for 113 thyroid antibody positive women, and 15 (13%) women had abnormal results. Four were hyperthyroid and 11 were hypothyroid. After excluding these women, there were 98 thyroid antibody positive women known to be euthyroid.

The pregnancies of the 98 thyroid antibody positive, euthyroid women were followed prospectively. Within the study period time interval, there were 24 pregnancies during which no treatment was given. Ten pregnancies were lost in the first trimester, the remaining 14 resulted in live births at term (58%). Among the 708 thyroid antibody negative women, there were 87 untreated pregnancies reported during the study period. Two women were lost to follow up and four of the pregnancies proved to be ectopic. Of the remaining 81 pregnancies, 30 miscarried in the first trimester, four miscarried in the second trimester, and 47 resulted in live births at term (58%).

There was no significant difference in age or past history of miscarriage between the thyroid antibody positive and negative groups within the whole study population or within the untreated pregnancy outcome group (see Table I).

### Table I. Demographic data of thyroid antibody positive versus negative women

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>Median age (range) (years)</th>
<th>Median no. past miscarriages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study population</td>
<td>870</td>
<td>34 (19–46)</td>
<td>4 (3–12)</td>
</tr>
<tr>
<td>Thyroid antibody negative</td>
<td>708</td>
<td>34 (19–46)</td>
<td>4 (3–12)</td>
</tr>
<tr>
<td>Thyroid antibody positive</td>
<td>162</td>
<td>34 (20–46)</td>
<td>4 (3–10)</td>
</tr>
<tr>
<td>Pregnancy outcome group</td>
<td>105</td>
<td>34 (22–46)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Thyroid antibody negative</td>
<td>81</td>
<td>34 (22–46)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Thyroid antibody positive</td>
<td>24</td>
<td>34 (20–41)</td>
<td>4 (3–6)</td>
</tr>
</tbody>
</table>

125 (19%) of the remaining 659 antiphospholipid antibody negative women. There was no correlation between thyroid antibody and antiphospholipid antibody status.

Thirteen (1.6%) of the 870 women had a past medical history of thyroid dysfunction, of whom 12 proved positive for TgAb and/or TmAb. All 13 were excluded from the pregnancy outcome study, although they had been treated, thus reducing the thyroid antibody positive group from 162 to 149 women. On reviewing data collected for this study since 1995, it was found that TSH results had not been recorded for all 149. Regrettably, no serum taken prior to pregnancy was available in 36 cases. TSH concentrations were performed for 113 thyroid antibody positive women, and 15 (13%) women had abnormal results. Four were hyperthyroid and 11 were hypothyroid. After excluding these women, there were 98 thyroid antibody positive women known to be euthyroid.

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### Discussion

An increased risk of reproductive failure has been reported in a variety of medical conditions which are now recognized to have an autoimmune basis, for example, systemic lupus erythematosus. Autoimmune disorders that affect reproductive processes are often subclinical and most women who present with repeated miscarriage are otherwise well (Gleicher et al., 1993). The higher prevalence of thyroid antibodies identified in euthyroid women with recurrent miscarriage has led to the assumption that these antibodies are linked to the women’s experience and will predict an increased risk of future miscarriage for them. It has been suggested that, in women with recurrent miscarriage, thyroid antibodies are a consequence...
not of thyroid dysfunction but of abnormal autoimmune activation (Lejeune et al., 1993). Thyroid antibodies may serve as peripheral markers of disordered T-cell function (Kim et al., 1998; Wilson et al., 1999).

Like thyroid antibodies, antiphospholipid antibodies have been noted to be more prevalent among women with recurrent miscarriage and are also thought to be a consequence of abnormal autoimmune activation. No correlation was identified between thyroid antibody status and antiphospholipid antibody status, which raises the possibility that they may be the result of different autoimmune abnormalities.

This study confirms previous reports that abnormal thyroid function is not associated with recurrent miscarriage (Harger et al., 1983; Lejeune et al., 1993; Kutteh et al., 1999). Fourteen women (1.6%) had known clinical thyroid disease and a further 15 with subclinical disease were newly diagnosed (1.7%). The total prevalence of 3.3% is similar to that expected in the general, female population (Rose and Mackay, 1998).

This study demonstrates that women with recurrent miscarriage in association with thyroid antibodies can be reassured that thyroid antibodies do not confer a worse prognosis in terms of their future pregnancy outcome. The untreated live birth rate for women in this study, whether thyroid antibody positive or negative, was 58%. This contrasts with the study by Pratt et al. (1993b) who reported a first trimester miscarriage rate of 14% in 29 recurrent miscarriers with no thyroid antibodies, a figure which rose to 62% in 13 women with thyroid antibodies. In the current study, the first trimester miscarriage rate among 81 recurrent miscarriers with no thyroid antibodies was 37%, which is similar to the 31% pregnancy loss rate previously reported by our centre in women with unexplained recurrent miscarriage (Clifford et al., 1997).

Pratt makes no comment on any treatment taken by the women in her study, all of whom had unexplained recurrent miscarriage. Although the pregnancy outcomes were followed of all 870 women initially tested for thyroid antibodies, only 111 took no treatment. There are considerable difficulties in offering only supportive care to women who have attended a tertiary care centre in the hope and expectation of treatment. It is common for these women to seek treatment on an empirical basis. They may take a variety of therapies, typically progesterone or low dose aspirin, either offered by their referring doctors or bought from the chemist on the basis of their own, often extensive, research.

It is concluded that the presence of thyroid autoantibodies does not affect the future pregnancy outcome of women with a history of recurrent miscarriage. Further to this, routine screening for thyroid antibodies is of no practical benefit in the investigation of recurrent miscarriage.

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References

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