Lack of association between thyroid autoantibodies and parity in a population study argues against microchimerism as a trigger of thyroid autoimmunity

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Abstract

Background: Thyroid autoimmunity is more common in females than in males. One possible explanation for this female preponderance may be the effect of oestrogens on the immune system. It has also been suggested that foetal microchimerism involving transfer of foetal cells into maternal tissue during pregnancy may play an important role.

Objective: We investigated the association between the presence of circulating thyroid autoantibodies and previous pregnancy, parity and the use of oral contraceptives (OCs) and hormone replacement therapy (HRT) in a population cohort.

Methods: We examined 3712 women randomly selected from the general population. Serum was analysed for thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (Tg-Ab) using assays based on an RIA technique (DYNO test). Data were analysed in logistic regression models to adjust for possible confounders. Women previously treated for thyroid disease or with pregnancy within 1 year prior to the study were excluded from the analyses.

Results: In both univariate and multivariate models and whether the presence of TPO-Ab and Tg-Ab was investigated alone or in combination, findings were negative with respect to an association between circulating thyroid antibodies and previous pregnancy, number of pregnancies, parity and previous abortion. There was no association between thyroid autoantibodies and use of OCs. Women aged 60–65 years receiving HRT now or previously had a lower prevalence of Tg-Ab (univariate, \( P = 0.01 \); multivariate, \( P = 0.02 \)). No such association was observed between HRT and TPO-Ab.

Conclusion: In this population study there was no association between previous pregnancy, parity and thyroid antibodies, which argues against the role of microchimerism as a trigger of thyroid autoimmunity. Exogenous oestrogens may reduce aspects of autoimmunity.

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Introduction

Autoimmune diseases are a poorly understood group of disorders. The regulatory malfunction of the immune system is often supposed to be secondary to a genetic predisposition currently thought to be multigenic (1). However, even in a genetically predisposed person, a triggering event is usually required for frank autoreactivity (2, 3). The character of this trigger is often unknown.

Autoimmune thyroiditis (AITD) is one of the most common autoimmune disorders. Like other thyroid diseases, AITD is more common in females than in males (4, 5). One possible explanation for this female predominance could be the effect of oestrogens on the immune system (6). Another possibility is that foetal microchimerism could contribute to the pathogenesis of AITD (6). This hypothesis is supported by the predominance of females but also by the fact that chronic graft-vs-host disease shares similarities with some autoimmune diseases (7).

Microchimerism is the presence of a mixture of a small number of cells from different individuals coexisting within tissue, including the peripheral blood. In foetal microchimerism, there is a transfer of cells or DNA from the foetus to the mother during pregnancy (8). Foetal-derived DNA has been found in maternal blood as early as in the first trimester (9) and up to 38 years after pregnancy (10). The foetal cells which remain in the maternal tissue after delivery may modu-
late AITD by playing a role in antigen presentation. If foetal microchimerism contributes to thyroid autoimmunity in women there would be an association between previous pregnancy and the presence of thyroid autoimmunity. We investigated the association between the presence of thyroid autoantibodies (thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (Tg-Ab)) in the circulation and previous pregnancies, parities, abortions and use of oral contraceptives (OCs) and hormone replacement therapy (HRT) in a population cohort.

**Subjects and methods**

**Study population**

This study was part of the Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr), which is the official clinical monitor of the Danish iodine supplementation programme. The present investigation took place before the initiation of iodine supplementation. This study population represents the female part of the DanThyr cohort, which has been described in detail previously (11).

A sample of females within the following age groups, young adults (18–22 years), mid-gestational age (25–30 years), premenopausal (40–45 years) and postmenopausal (60–65 years) living in either Aalborg, Northern Jutland or Copenhagen, was drawn from the Civil Registration System. The subjects were given random numbers within each group with the help of computer software and were invited to the study examination in the order of the random numbers. The number of subjects invited in each group was adjusted throughout the study period to obtain uniform numbers of participants in all groups. The participants were invited by letter. When no response was received a new invitation was sent by mail. Of the 7286 subjects invited, 3712 (50.9%) participated in the study examination. The age distribution of the participants was homogenous in the two subcohorts.

Within the two geographically delimited areas the median iodine concentrations in spot urine were 45 μg/l (Aalborg) and 61 μg/l (Copenhagen) after the exclusion of subjects taking iodine supplementation (53 μg/l and 68 μg/l in all subjects) (12).

**Data collection**

The participants answered questionnaires concerning previous treatment for thyroid disease and smoking habits and an obstetric anamnesis including the number of previous pregnancies, parities and abortions either spontaneous or provoked. Previous or present use of OCs and HRT was registered. Blood samples were collected.

**Laboratory procedures**

Serum TPO-Ab and Tg-Ab were both measured by RIA (DYNO test anti-TPO and DYNO test anti-Tg; BRAHMS Diagnostica, Berlin, Germany). The assays and evaluation of cut-off values have been described in detail previously (4). The following detection limits were used: TPO-Ab > 30 U/l; Tg-Ab > 20 U/l both corresponding to the functional sensitivity given by the manufacturer.

**Statistical analysis and distribution of variables**

All data processing was performed with SPSS 10.0 software (SPSS Inc. Chicago, Illinois, USA). The association between the presence of thyroid autoantibodies (TPO-Ab and Tg-Ab) in serum and previous pregnancies, parities, abortions and use of OCs or HRT were analysed in logistic regression models to allow adjustment for possible confounding by other factors.

The prevalence of thyroid antibodies increases with age in women as does the number of previous pregnancies. Thus age would confound the evaluation of association between thyroid antibodies and previous pregnancy, and age group was included in all simple regression models. Because of the different distribution of the use of OCs and HRT and of smoking between the two regions and age groups, we included age group, smoking and region in the multivariate models.

Women who had been treated for thyroid disease (n = 207) or who were or had been pregnant within the last 12 months (n = 144) and cases with missing measurements of TPO-Ab or Tg-Ab (n = 78) were excluded, leaving 3283 cases for analysis. The analyses of the use of OCs included only women aged 18–45 years and the analyses of the use of HRT only women aged 60–65 years.

The distribution of some of the central variables is shown in Table 1. The level of significance was set at 5%.

The study was approved by the regional Ethics Committees in Northern Jutland and Copenhagen and all participants gave written informed consent.

**Results**

The prevalence rates of TPO-Ab and Tg-Ab increased with increasing age (Table 2).

There was no association between the presence of thyroid autoantibodies (TPO-Ab and/or Tg-Ab) in serum and previous pregnancy, parity and provoked or spontaneous abortion (Fig. 1). In a multivariate model which included smoking and region we still found no association between TPO-Ab and/or Tg-Ab and previous pregnancy, parity and abortion (previous pregnancy: OR (CI) 0.92 (0.72–1.17); parity: 1.02 (0.85–1.12); spontaneous abortion: 1.07 (0.83–1.38); provoked abortion: 0.99 (0.78–1.25)).
The risk of having thyroid antibodies (TPO-Ab and/or Tg-Ab) was similar in women who had never been pregnant compared with women with one or more previous pregnancies and in women who had never given birth compared with women with one or more previous childbirths (Fig. 2). However, in the simple model, women with one parity had a tendency for a lower risk of having thyroid autoantibodies measured in serum compared with nullipara (one/no parity, OR (CI): 0.81 (0.60–1.10) and a significantly lower risk compared with women with two, three or more previous parities (one/two parities: OR (CI): 0.74 (0.55–0.98); one/three parities: 0.67 (0.48–0.93). This tendency was confirmed in the multivariate model (one/two parities: OR (CI): 0.75 (0.56–1.01); one/three parities: 0.69 (0.50–0.96)).

There was no association between previous pregnancy and elevated thyrotrophin (TSH) in women with TPO-Ab and/or Tg-Ab measured in the serum. However, in women without thyroid autoantibodies, elevated TSH was more frequent in women without any pregnancies compared with women with previous pregnancies when data were analysed in a logistic regression model adjusting for age group (P = 0.02).

The association between the use of OCs and thyroid autoantibodies (TPO-Ab and/or Tg-Ab) was tested only in women aged 18–45 years. We found no association between the present use of OCs and thyroid autoantibodies and ever having used OCs and thyroid autoantibodies either in simple logistic regression models (Fig. 3) or in multivariate models (present use of OC, OR (CI): 0.92 (0.72–1.17); ever having used OCs: 0.88 (0.65–1.20)).

The association between HRT and thyroid autoantibodies was tested in postmenopausal women aged 60–65 years. In a simple logistic regression model, we found a negative association between TPO-Ab and/or Tg-Ab and present use of HRT (Fig. 4). When smoking and region were included in the multivariate models, the association between present use of HRT and thyroid autoantibodies was still significant (OR (CI): 0.63 (0.40–0.97). However, the association between use of HRT at menopause and the presence of TPO-Ab and/or Tg-Ab became statistically insignificant (OR (CI): 0.72 (0.51–1.02)). To study the effect of HRT in more detail we tested the use of HRT against different

Table 1 Distribution of variables in the 3283 women from the population studied.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>18–22 years (n = 897)</th>
<th>25–30 years (n = 800)</th>
<th>40–45 years (n = 859)</th>
<th>60–65 years (n = 727)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies</td>
<td>None</td>
<td>802</td>
<td>456</td>
<td>94</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>73</td>
<td>178</td>
<td>138</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Two</td>
<td>16</td>
<td>103</td>
<td>264</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td>Three or more</td>
<td>6</td>
<td>63</td>
<td>363</td>
<td>365</td>
</tr>
<tr>
<td>Childbirths</td>
<td>None</td>
<td>878</td>
<td>590</td>
<td>148</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>One</td>
<td>14</td>
<td>125</td>
<td>211</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Two</td>
<td>4</td>
<td>75</td>
<td>374</td>
<td>266</td>
</tr>
<tr>
<td></td>
<td>Three or more</td>
<td>1</td>
<td>10</td>
<td>126</td>
<td>262</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>Yes</td>
<td>15</td>
<td>59</td>
<td>221</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>882</td>
<td>741</td>
<td>638</td>
<td>583</td>
</tr>
<tr>
<td>Provoked abortion</td>
<td>Yes</td>
<td>73</td>
<td>185</td>
<td>312</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>851</td>
<td>615</td>
<td>547</td>
<td>561</td>
</tr>
<tr>
<td>OC now</td>
<td>Yes</td>
<td>551</td>
<td>328</td>
<td>75</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>346</td>
<td>472</td>
<td>784</td>
<td>–</td>
</tr>
<tr>
<td>OC ever</td>
<td>Yes</td>
<td>729</td>
<td>737</td>
<td>762</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>168</td>
<td>62</td>
<td>96</td>
<td>–</td>
</tr>
<tr>
<td>HRT at menopause</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>423</td>
</tr>
<tr>
<td>HRT now</td>
<td>Yes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>556</td>
</tr>
</tbody>
</table>

Table 2 Prevalence rates (%) of TPO-Ab and Tg-Ab in women of various ages. Prevalence rate of different combinations of thyroid antibodies in the four groups of women with no current or previously treated thyroid disease or pregnancy within the last 12 months.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number</th>
<th>TPO-Ab and/or Tg-Ab</th>
<th>TPO-Ab (%)</th>
<th>Tg-Ab (%)</th>
<th>TPO-Ab and Tg-Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–22</td>
<td>897</td>
<td>12.3</td>
<td>7.4</td>
<td>9.1</td>
<td>4.2</td>
</tr>
<tr>
<td>25–30</td>
<td>800</td>
<td>18.2</td>
<td>12.0</td>
<td>14.0</td>
<td>7.8</td>
</tr>
<tr>
<td>40–45</td>
<td>859</td>
<td>24.9</td>
<td>19.1</td>
<td>15.8</td>
<td>10.0</td>
</tr>
<tr>
<td>60–65</td>
<td>727</td>
<td>29.7</td>
<td>21.7</td>
<td>20.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Total</td>
<td>3283</td>
<td>20.9</td>
<td>14.7</td>
<td>14.5</td>
<td>8.3</td>
</tr>
</tbody>
</table>
combinations of thyroid autoantibodies in serum (Fig. 5). There was no association between HRT and the presence of TPO-Ab, but a clear association between HRT and a low risk of having Tg-Ab (Fig. 5).

Sensitive antibody assays were used for this study and we included participants with low levels of thyroid antibodies in serum as the positive. To evaluate participants with higher levels of antibody only, all data were re-analysed in logistic regression models using 100 U/ml as cut-off for both the TPO-Ab and the Tg-Ab assay. The prevalence rate of thyroid antibody above this level was: TPO-Ab and/or Tg-Ab; women aged 18–22 years: 6.7%; 25–30 years: 10.5%; 40–45 years: 14.9%; 60–65 years: 19.0%.

Discussion

In this random sample of 3283 women from the general population without previous thyroid disease or pregnancies 1 year prior to the study, we found no association between the presence of circulating thyroid autoantibodies and previous pregnancy, parity and abortion. There was no association between thyroid autoantibodies and treatment with OCs ever or now as 1 was included in the confidence intervals. Similar results were seen when data were analysed in multivariate models.

Again we found no association between the presence of TPO-Ab and/or Tg-Ab in serum and previous pregnancy (OR (CI)): 0.94 (0.70–1.26); previous parity: 1.02 (0.76–1.37); spontaneous abortion: 0.97 (0.71–1.31); provoked abortion: 1.06 (0.81–1.40); present treatment with OCs: 0.85 (0.62–1.16); ever having used OCs: 0.83 (0.57–1.20). The association between the presence of Tg-Ab and the use of HRT at menopause became statistically insignificant.
between microchimerism and AITD, and the results
higher in women with previous pregnancies compared
(TPO-Ab and/or Tg-Ab) would be expected to be
of AITD the prevalence of thyroid autoantibodies
foetal tissue (7).

The circumstances necessary for these foetal-derived
merism often occurs in normal pregnancies (17, 18).
known past male pregnancy , indicating that microchi-
R was negative,
was demonstrated in peripheral blood from 30 – 34% of healthy women with a
y age suggests that pregnancy-related factors could have
development of AITD. These factors could be hormonal, but it has also been suggested that
es and other unidentiﬁed
mercials might be important in the
pathogenesis of AITD and other autoimmune diseases including scleroderma (6, 14, 15).

A relatively simple method to detect microchimerism
is to demonstrate male-speciﬁc gene markers in women
who have been pregnant with a male child (16). Male-
speciﬁc gene markers have been demonstrated in per-
ipheral blood from 30 – 34% of healthy women with a
own past male pregnancy, indicating that microchi-
erism often occurs in normal pregnancies (17, 18).
The circumstances necessary for these foetal-derived
cells to become established and expand and further-
more migrate to interact with multiple tissues includ-
ing the thyroid are unknown. It is likely, however, that genetic, environmental and other yet-unidentiﬁed
ctors combine to determine the persistence of the
foetal tissue (7).

If microchimerism is important in the pathogenesis of
ITD the prevalence of thyroid autoantibodies
(TPO-Ab and/or Tg-Ab) would be expected to be
in women with previous pregnancies compared
women without any pregnancies. The present
study does not support this idea.

Relatively few studies have tested the association
between microchimerism and AITD, and the results
are not equivocal. In a case-control study of 89
women with Hashimoto’s thyroiditis. Phillips et al.
(19) found no evidence of an association between
Hashimoto’s thyroiditis and previous parity, and no
trend to an increasing disease risk with an increasing
number of parities. On the other hand, some studies
support the hypothesis of a link between microchimer-
erism and AITD. Klintschar et al. (20) detected microchi-
erism in the thyroid in eight out of 17 patients
suffering from Hashimoto’s disease compared with
only one out of 25 controls with nodular goitre. The
study group and control group had comparable num-
er of pregnancies and sons. In a study by Renne
et al. (21) of 49 women, who all had sons, microchi-
erism was found in the thyroid from 23 out of 40
women with AITD (Hashimoto’s disease: n = 25;
Graves’ disease: n = 15), compared with two out of
ine women with thyroid adenoma. Srivatsa et al.
(22) detected microchimerism in 12 out of 20 thyroids
from women who had sons and who had undergone
thyroidectomy for various thyroid diseases (nodular
goitre: n = 9; AITD: n = 11). Four out of the 12 thy-
roids containing male cells were classiﬁed as nodular
goitre. In only eight out of the 11 thyroids classiﬁed
as AITD could microchimerism be detected. In the
control group, consisting of eight thyroids taken
from women who had died from other disorders,
microchimerism was detected in none. Accordingly,
at least three studies suggest a relation between
microchimerism and AITD (20–22) or at least
between microchimerism and thyroid disease (22).
However, the role of microchimerism is unlikely to be
essential for developing AITD as microchimerism was
not detected in 25 – 48% of the patients with AITD. It is
possible that the difference in the prevalence of microchi-
erism between patients and the control groups might
result from general immunological differences and per-
haps differences in the leakiness of the placenta during
pregnancy. Therefore this microchimerism might be
not the cause for – but the consequence of – a pre-exist-
ing subclinical autoimmune disease involving the pla-
enta (20). It might also be speculated that a thyroid
affected by autoimmunity would give better possibilities
of survival of foetal cells trapped in the thyroid during
pregnancy.

A number of studies have dealt with microchimerism
in women with scleroderma. Most of the studies have
not been able to show an increased prevalence of micro-
chimerism in women suffering from scleroderma com-
pared with controls. In a hospital based study of 46
women with scleroderma, Pisa et al. (23) even found a
reduced risk of scleroderma with previous parity. The
risk decreased with increasing numbers of children.
Nelson et al. (15) demonstrated that the prevalence of
male cells was not higher in women with scleroderma
compared with controls. On the other hand, the concen-
tration of male DNA in women with scleroderma was
higher than in healthy controls.

No association between thyroid autoantibodies and parity

Figure 5 The association between different combinations of
thyroid autoantibodies in serum and use of HRT at menopause.
Figures are ORs with 95% CIs from six multivariate logistic
regression models. Participants without the specific antibody com-
ination are used as a reference in each case. HRT was nega-
tively associated with Tg-Ab measured either alone or together
with TPO-Ab. There was no association between use of HRT at
menopause and the presence of TPO-Ab.

with women who were not treated with HRT. This
association was confmed to Tg-Ab whereas there was
no association with TPO-Ab.

Circulating thyroid autoantibodies are more
common in females than in males (4, 5). The reason
for this female preponderance is unclear. Hormonal
and genetic factors may play a role as girls with Turn-
er’s syndrome (X0 karyotype) are more often affected
by thyroid autoimmunity (13). The high prevalence
of thyroid autoimmunity in women after child-bearing
age suggests that pregnancy-related factors could have
an influence on the development of AITD. These factors
could be hormonal, but it has also been suggested that
foetal microchimerism might be important in the
pathogenesis of AITD (21, 22, 23, 24). Some studies
have reported an increase in the prevalence of microchi-
erism often occurring in normal pregnancies (17, 18).
The circumstances necessary for these foetal-derived
cells to become established and expand and further-
more migrate to interact with multiple tissues includ-
ing the thyroid are unknown. It is likely, however, that genetic, environmental and other unidentiﬁed
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tration of male DNA in women with scleroderma was
higher than in healthy controls.

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Immune suppression during pregnancy suggests that high levels of endogenous oestradiol may prevent autoimmunity. There are relatively few studies concerning the association between exogenous oestrogens and thyroid autoimmunity and the results are dissimilar. In the present study, we found no association between OCs and thyroid autoantibodies, whereas HRT was negatively associated with Tg-Ab but not with TPO-Ab. There are, however, some studies suggesting that OCs could be protective against the development ofAITD. In a large study of 46,000 women, the overall prevalence of hypo- and hyperthyroidism was less frequent among OC users than controls (24). Vestergaard et al. (25) found that ever having used OCs was associated with a slightly lower risk of Graves’ disease but not of Hashimoto’s disease. In a cohort study of 803 subjects at risk of developing AITD, Strieder et al. (26) found that the use of oestrogen was negatively correlated with the presence of TPO-Ab. In a follow-up study of healthy middle-aged women, Massoudi et al. (27) found no difference in antibody level in postmenopausal women using HRT compared with women who did not (27).

These discrepancies in association between thyroid autoantibodies and exogenous oestrogens may be explained by the different methods applied and especially differences in the sensitivity of the antibody assays used.

In conclusion, it has been shown in a number of studies that foetal cells, circulating in the pregnant woman, may be trapped and survive for years in the thyroid of the mother. However, we find no evidence that such a mechanism is of importance for the high prevalence of thyroid autoimmunity in women in the population.

Acknowledgements

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