Thyroid autoimmunity and thyroid dysfunction in women with endometriosis

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BACKGROUND: Women with endometriosis may have higher rates of autoimmune disorders, including hypothyroidism. The objective of this study was to compare the prevalence of thyroid dysfunction and autoimmune thyroid disease (AITD) between women with endometriosis and a control group. METHODS: This was a cross-sectional study carried out in 148 women with surgically confirmed endometriosis and 158 controls. The mean age of the study group was 34.6 (7.1 SD) years (range 21–42) and 32.1 (7.7 SD) years (range 18–44) for controls. Serum levels of thyroid-stimulating hormone, free thyroxine and the anti-thyroperoxidase and anti-thyroglobulin antibodies were evaluated. RESULTS: Thyroid disorders were identified in 20.9% of the endometriosis group and 26.5% of the control group (P = 0.25). The overall frequency of thyroid dysfunction was 12.2% and 10.8% for the endometriosis and control groups, and the frequency of positive thyroid antibodies, 14.9% and 22.2%, respectively (P = 0.20). Endometriosis stage and infertility history were not associated with thyroid dysfunction and AITD in the study group. CONCLUSIONS: The prevalence of thyroid dysfunction and AITD was similar in the two study groups. Screening for thyroid disturbances in women with endometriosis is not indicated.

Keywords: endometriosis; autoimmune thyroid disease; hypothyroidism; diagnosis

Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction (Kennedy et al., 2005). Retrograde menstruation proposed by Sampson (1927) is still one of the most accepted theories; however, it fails to explain why nearly all women of reproductive age have some degree of retrograde menstruation (Halme et al., 1984), while only a small percentage develop endometriosis. It has been postulated that other factors, particularly immunological factors, may cause the endometrial tissue displaced by retrograde menstruation to develop into ectopic lesions (Nothnick, 2001). Endometriosis is associated with the presence of a variety of autoantibodies (Gleicher et al., 1987) and fulfills most of the classification criteria for an autoimmune disease, such as tissue damage, polyclonal B lymphocyte activation, T-lymphocyte immunological abnormalities, B-lymphocyte immunological abnormalities, preponderance of females, multiorgan involvement, occurrence in families and possible genetic and environmental factors, besides the association with other autoimmune diseases (Nothnick, 2001).

A large cross-sectional survey conducted in the USA by the Endometriosis Association (Sinaii et al., 2002), based on self-reported information obtained from mailed questionnaires, found that women with endometriosis had significantly higher rates of autoimmune disorders, including hypothyroidism (9.6% versus 1.5% in the general population). This study, however, had some methodological limitations since data were obtained from self-administered questionnaires and the prevalence of the disease in the general population used for comparison was not limited either to women or to those of reproductive age.

To determine whether women with endometriosis are at a greater risk of thyroid autoimmune disease or thyroid dysfunction, this study evaluated the prevalence of these disorders in women with endometriosis compared with a control group of women of reproductive age.

Materials and Methods

This was a cross-sectional study carried out at the Department of Obstetrics and Gynaecology, School of Medicine, Universidade Estadual de Campinas, Campinas, Brazil, between December 2005 and May 2006. The University’s Institutional Review Board approved the protocol, and all women signed an informed consent form.

A total of 148 women with surgically and histopathologically confirmed endometriosis receiving care at the endometriosis outpatient unit were included in this study. The diagnosis of endometriosis was based on laparoscopy with histopathological confirmation of the lesions identified. The control group consisted of 158 healthy women of reproductive age, matched by age and parity. The exclusion criteria for both groups were a history of thyroid disease or other autoimmune diseases, pregnancy, and the use of medications known to affect thyroid function or autoimmune disorders.
clinic were included in the study group, whereas a control group consisted of 158 women from a family planning clinic, who had no history of endometriosis and no endometriosis-related symptoms. All the women in this study were enrolled consecutively during their regular scheduled visit to the clinic.

The questionnaire included data on socio-demographic characteristics (age, ethnicity, years of formal school education), medical history including infertility and number of spontaneous abortions, smoking habit, contraceptive methods and other medication currently in use. In the study group, the stage of endometriosis was obtained from the patient’s medical records and was classified according to the definitions of the American Society for Reproductive Medicine (1997). Participants were also asked if they had ever been diagnosed or suspected of having hypothyroidism or hyperthyroidism, Hashimoto’s thyroiditis or Graves’ disease. If they had ever undergone a fine needle aspiration biopsy of the thyroid or a surgical thyroid resection of any kind, they were requested to submit the cytological or histological findings. The most common symptoms of hypothyroidism, such as fatigue, depression, difficulty in losing weight or a weight gain in the last 12 months, dry skin, weakness, constipation and intolerance to cold, were evaluated.

The following serum measurements were performed: thyroid-stimulating hormone (TSH, standard reference range 0.4–4.0 mU/l), intra-assay variation: 13.8%, inter-assay variation: 17.5%; free thyroxine (T4, reference range 0.8–1.9 ng/dl), intra-assay variation: 6.8%, inter-assay variation: 7.8%; free triiodothyronine (T3, reference range 1.5–4.1 ng/l), intra-assay variation: 13.2%, inter-assay variation: 15.6%, anti-thyroperoxidase antibody (TPO-Ab, reference values <35 IU/ml), intra-assay variation: 4.3%, inter-assay variation: 10.5% and antithyroglobulin antibody (TgAb, reference value <49 IU/ml), intra-assay variation: 2.3%, inter-assay variation: 8.1%. All measurements were performed using an Immulite® 1000 chemiluminescent analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA).

Thyroid disorders were classified as follows:

(i) normal thyroid function: defined as TSH, free T4 and T3 values within the standard reference ranges;
(ii) autoimmune thyroid disease (AITD): euthyroid according to clinical and laboratory parameters, with elevated serum levels of TPO-Ab and/or Tg-Ab;
(iii) overt hypothyroidism: elevated TSH with reduced free T4 levels;
(iv) subclinical hypothyroidism: elevated TSH, usually below 10 IU/ml, and normal free T4 and free T3;
(v) autoimmune hypothyroidism or subclinical hypothyroidism: conditions associated with the presence of antithyroid antibodies, either one or both together;
(vi) thyrotoxicosis (or hyperthyroidism): low TSH and elevated free T4 and/or free T3;
(vii) subclinical hyperthyroidism: low TSH and normal free T4 and/or free T3;
(viii) autoimmune hyperthyroidism or subclinical hyperthyroidism: conditions associated with the presence of antithyroid antibodies, either one or both together (www.thyroidmanager.org).

Sample size was estimated at a minimum of 124 women per group to identify the difference reported by Sinaii et al. (2002) (9.6% and 1.5% hypothyroidism in endometriosis group and control, respectively) with a 5% significance level. The association of the independent variables and the study group with thyroid disorder (dysfunction + positive antibodies) and thyroid dysfunction (clinical alterations) was assessed using the chi-square test and Fisher’s exact test. The prevalence of thyroid disorders and thyroid dysfunction among women with endometriosis was calculated and compared with that of the control group using the Mann–Whitney test and the odds ratios, calculated with their 95% confidence intervals. The software program used for all statistical analyses was SAS, version 8.2 (SAS Institute, Cary, NC, USA). Statistical significance was established at 5%.

**Results**

The mean age of women in the study group was 34.6 (SD ± 7.1) years and 32.1 (SD ± 7.7) years for women in the control group (P = 0.0053). There were no statistically significant differences in mean body mass index in the study and control groups (26.1 versus 26.6 kg/m², respectively) or smoking habits and the majority of women had never smoked (74.3% versus 74.1%, respectively).

In the study group, 70 (47.3%) reported infertility (mean duration of infertility was 6.2 years), 56 women (37.8%) were nulligravidas, 62 (41.9%) of these women had never delivered, and mean parity was 0.8. In the control group, all the women had conceived spontaneously and given birth at least once. Mean parity was 2.4 and all women were using a contraceptive method.

The frequency of each diagnosis in each group is presented in Table 1. The diagnoses have been summarized into four categories: (i) no thyroid disorder, (ii) AITD, (iii) hypothyroidism and (iv) hyperthyroidism. Women on L-thyroxin replacement therapy, who self-reported hypothyroidism, were considered hypothyroid even if their hormone levels were within the normal range. Thirty-one of the 148 women in the endometriosis group (20.9%) were identified as having thyroid disorder, whereas in the control group, 42/158 women (26.5%) were found to have thyroid disorder (Table 1).

The overall frequency of thyroid dysfunction was 12.2% (18 cases of overt or subclinical hypothyroidism) among the group of women with endometriosis and 10.8% (12 cases of hypothyroidism and 5 of hyperthyroidism, either overt or subclinical) in women in the control group (Table 2).

The frequency of positive thyroid antibodies (TPO-Ab+) and/or Tg-Ab+) was 14.9% among women with endometriosis and 22.2% in the control group (Table 3).

All symptoms usually related to thyroid dysfunction were significantly more frequent among women with endometriosis except constipation (P = 0.22) and dry skin (P = 0.08) (data not shown).

No increased risk for AITD (P = 0.752) or for thyroid dysfunction (P = 0.6113) was found for women with endometriosis stage I and II versus III and IV (data not shown).

No increased risk for AITD (P = 0.20) or for thyroid dysfunction (P = 0.51) was found in the endometriosis group comparing those with infertility versus those without infertility history (data not shown).

**Discussion**

Our results showed no significant increase in thyroid disease in women with endometriosis. The overall frequency of thyroid dysfunction was 12.2% (18 cases of overt or subclinical hypothyroidism) in women with endometriosis and
10.8% (12 cases of hypothyroidism and 5 of hyperthyroidism, either overt or subclinical) in women in the control group. According to these results, the female population with endometriosis is not at a higher risk of having thyroid disease, and screening for this problem is not, therefore, justified in these women.

Regarding AITD, the prevalence in the control group was 15.8% compared with 8.8% in women with endometriosis. This difference was not statistically significant. Likewise, 10 of the 17 cases of thyroid dysfunction in the control group were associated with the presence of antithyroid antibodies (58.8%), whereas in the group of patients with endometriosis,
9/18 (50%) cases of thyroid dysfunction were positive for antithyroid antibodies.

In a 20-year follow-up study, the Whickham survey showed that the annual risk for spontaneous hypothyroidism was 5% in women who had raised serum TSH values and who were positive for antithyroid antibodies, 3% if only serum TSH was raised and 2% if only antithyroid antibodies were positive: the cumulative incidence of hypothyroidism over 20 years was 55%, 33% and 27%, respectively. The chance of a woman developing hypothyroidism increases linearly once serum TSH is above 2 mU/l. That chance is further increased if the woman is positive for antithyroid antibodies and decreased if she is negative (Vanderpump et al., 1995).

Our findings for the percentage of women affected by thyroid disease is within the expected range for the Brazilian female population of reproductive age. Prevalence studies in Brazil have reported incidences ranging from 6.6% to 14.1% for thyroid dysfunction and 9.1% to 19.5% for autoimmune disease (Mendonça and Jorge, 2002; Camargo et al., 2006).

The results of the present study differ from those reported by Sinaii et al. (2002), who concluded that women with endometriosis have a higher rate of hypothyroidism compared with the published rates of hypothyroidism in the general US female population (9.6% versus 1.5%, published rates of hypothyroidism in the general US female population). Although that study has considerable strength, mainly due to the large sample size (n = 3680), it also has remarkable limitations attributable to the self-reported mail surveys (Bergmann et al., 1998). These limitations include the possibility that women may have misinterpreted questions, may not have recognized the name of specific diseases and that some women already had undiagnosed hypothyroidism at the time they answered the questionnaire. Moreover, according to the authors, due to insufficient US data, the prevalence estimated for Hashimoto’s thyroiditis/hypothyroidism also included data from international studies and not from a control group; these studies were not restricted to women and certainly included older women with different characteristics from those of the study population. It is also possible to speculate that women with symptoms of thyroid disease may have suspected that they had thyroid disease when they actually did not.

In our study, complaints of almost all symptoms, usually related with hypothyroidism, were statistically more frequent among women with endometriosis and were not in fact associated with thyroid dysfunction. However, the presence of the disease was not confirmed by laboratory tests; therefore, the symptoms of thyroid dysfunction were not predictive of the disease. A high prevalence of depression and impairment of quality of life, including physical and emotional aspects, in women with endometriosis has been previously demonstrated by our group (Marques et al., 2004; Lorençatto et al., 2006).

The strength of the current study is that the diagnoses of hypothyroidism, hyperthyroidism andAITD were investigated by serum measurements of thyroid hormone and antithyroid antibodies in accordance with strict criteria, and the study did not simply rely on information provided by the patients. Furthermore, the control group consisted of women from the same geographical region with similar demographic characteristics.

In addition, the women in the study group were older than the control group. The presence of thyroid autoimmunity and hypothyroidism increase with age; therefore, the lack of differences in the incidence of these conditions between the endometriosis and the control groups gives more strength to the study because the older endometriosis group would be expected to have a higher incidence of both thyroid problems.

One limitation of our study is that some of the women in the control group may have endometriosis. However, these are low-risk women, since all are parous and have no symptoms related to endometriosis and/or infertility.

In our study, the history of infertility was not associated with thyroid dysfunction orAITD. This finding is not in agreement with the 29% prevalence of positive antibodies observed in women with endometriosis and infertility described by Poppe et al. (2002), the highest prevalence among the female causes of infertility. The possible bias is that the evaluation carried out in our population was a secondary analysis and not the primary objective of the study; hence, sample size could have affected the findings. However, future studies evaluating specifically the subgroup of women with endometriosis and infertility may be necessary.

In addition, no association was found between severity of the disease and the prevalence of thyroid dysfunction orAITD; hence, screening based on the severity of the disease is also not recommended.

In conclusion, these findings show that women with endometriosis have no increased risk of thyroid dysfunction orAITD; therefore, screening tests for thyroid disease in women with endometriosis are unnecessary.

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References


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