Menstrual disturbances in various thyroid diseases

Yoko Kakuno, Nobuyuki Amino, Maki Kanoh, Miho Kawai, Miyuki Fujiwara, Misao Kimura, Ayako Kamitani, Kaori Saya, Reiko Shakuta, Sanae Nitta, Yasuko Hayashida, Takumi Kudo, Sumihisa Kubota and Akira Miyauchi

Kuma Hospital, Center for Excellence in Thyroid Care, Kobe 650-0011, Japan

Abstract. The prevalence of menstrual disturbances, including secondary amenorrhea, hypomenorrhea, oligomenorrhea, hypermenorrhea, polymenorrhea and irregular menstrual cycle were prospectively examined in 586 patients with hyperthyroidism due to Graves’ disease, 111 with hypothyroidism, 558 with euthyroid chronic thyroiditis, 202 with painless thyroiditis and 595 with thyroid tumor. In the overall patient group, the prevalence did not different from that in 105 healthy controls. However, patients with severe hyperthyroidism showed a higher prevalence of secondary amenorrhea (2.5%) and hypomenorrhea (3.7%) than those (0.2% and 0.9%, respectively) with mild or moderate hyperthyroidism. Moreover, patients with severe hypothyroidism had a higher prevalence (34.8%) of menstrual disturbances than mild-moderate cases (10.2%). Menstrual disturbances in thyroid dysfunction were less frequent than previously thought.

Key words: Hyperthyroidism, Hypothyroidism, Menstrual disturbance, Amenorrhea

IT has been reported that thyroid dysfunction is frequently associated with menstrual disturbances. Amenorrhea was one of the earlier known clinical changes associated with hyperthyroidism, as reported by von Basedow in 1840 [1]. Since then, amenorrhea has frequently been reported, along with a number of other changes in the menstrual cycle, including oligomenorrhea, hypomenorrhea and anovulation. These disturbances have been reported in more than half the patients with hyperthyroidism [2, 3].

On the other hands, hypermenorrhea and polymenorrhea have also been reported in about 50–80 % of patients with hypothyroidism [2-4]. These changes are sometimes related to ovulatory disturbance and subsequent infertility [5, 6] and thus clinicians have focused on these problems for long time.

However, these previous studies were performed in the 1950s and 1960s in a small number of patients with thyroid dysfunction. Krassas et al. reevaluated the prevalence of menstrual disturbances both in hyperthyroidism and hypothyroidism in 1994 and 1999, respectively, and found that thyroid dysfunction was less frequently associated with menstrual irregularities than previously considered [7, 8].

In this study, we prospectively studied 2052 patients with various thyroid diseases and examined menstrual disturbances, including secondary amenorrhea, hypomenorrhea, oligomenorrhea, hypermenorrhea, polymenorrhea and irregular menstrual cycle, and compared with those in healthy controls.

Patients and Methods

Patients

We prospectively investigated untreated female patients who attended the out patient clinic in Kuma Hospital and were in the reproductive age between 20 and 45 years old. Thyroid diseases were diagnosed according to the Diagnostic Guidelines of the Japan Thyroid Association (http://thyroid.umin.ac.jp/en/frame.html). As for thyroid dysfunction, 586 patients with hyperthyroidism due to Graves’ disease and 111 patients with hypothyroidism were examined. For comparison to control patients, we further examined 558 euthyroid patients with chronic thyroiditis, 202 patients with painless thyroiditis and 595 patients with thyroid tumor (489 benign and 106 malignant tumors).
Comparison of frequencies between patient groups and healthy controls was analyzed using Fisher’s exact probability test or chi-square test. Differences were considered significant at $p<0.05$.

**Results**

Prevalence of secondary amenorrhea, hypomenorrhea, oligomenorrhea, polymenorrhea and irregular menstrual cycle in patients with hyperthyroidism, hypothyroidism, chronic thyroiditis, painless thyroiditis and thyroid tumor were summarized in Table 2, and these data are compared with those of healthy controls. The prevalence of any of these disturbances was never significantly higher than that of healthy controls. When the groups of euthyroid chronic thyroiditis, thyroid tumor and healthy controls were combined to one group of euthyroid controls (n=1258), menstrual disturbances were found in 197 subjects (15.7%). This frequency was not different from that in hyperthyroidism.

Menstrual disturbances were analyzed in relation to the severity of hyperthyroidism. There were no differences in these disturbances between the groups of mildly or moderately elevated T4 and severely elevated T4 (Table 3). Similarly, hyperthyroid patients were divided into two groups based on serum FT3 levels. Severe group (FT3 30 pg/mL and more) had a significantly higher prevalence of secondary amenorrhea (2.5%) than that (0.2%) among those with mild or moderate hyperthyroidism (FT3 less than 30). Total frequency of menstrual disturbances was found in 23.5% of severe hyperthyroidism and this was significantly higher than that (16.3%) of mild or moderate hyperthyroidism (Table 3). Moreover, prevalence of hypomenorrhea (3.7%) in the severe group was significantly higher than that among healthy controls (0%). Influence of estimated disease duration was analyzed, but there were no differences between groups divided
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was significantly higher than that in the mild or moderate group (10.2%) (Table 5).

Discussion

It has long been thought that thyroid dysfunction was frequently associated with menstrual disturbances. However, in this study, the prevalence of men-
trual disturbances in patients with hyperthyroidism and hypothyroidism, including secondary amenorrhea, hypomenorrhea, oligomenorrhea, hypermenorrhea, polymenorrhea and irregular menstrual cycle, was not different from those in healthy controls.

The most impressive report in hyperthyroidism due to Graves’ disease was the presence of secondary amenorrhea described by Dr. von Basedow in 1840 [1]. Since then, it has generally been considered that there is a high frequency of amenorrhea in patients with Graves’ disease. In 1952, Goldsmith et al. found amenorrhea in 3 of 18 (16.7%) patients with Graves’ disease and, moreover, they found hypomenorrhea in 14 (77.8%) patients [2]. They finally found menstrual disturbances in 94.4% of patients. In 1955, Benson et al. examined 221 patients with Graves’ disease and amenorrhea was found in 10 (4.5%) patients. Hypomenorrhea and/or oligomenorrhea were found in 130 (58.8%) patients [3]. Unfortunately these two studies did not examine the healthy controls and they may have examined only typically severe cases of Graves’ disease, since diagnostic laboratory tests were not well advanced at that time. In 1993, Joshi et al. studied 68 patients with hyperthyroidism and found 3 cases (4.4%) of amenorrhea [10]. They also found 30 patients (44.1%) with hypomenorrhea/oligomenorrhea and this prevalence was significantly higher than that among healthy controls (8.1%). In 1994, Krassas et al. examined 214 patients with hyperthyroidism but they could not find any patients with secondary amenorrhea [7]. Moreover, the frequencies of hypomenorrhea, oligomenorrhea, hypermenorrhea, and polymenorrhea did not differ from those of normal controls.

Summarizing these data in hyperthyroidism, studies were reported in the 1950s and 1960s and but not sufficient because of the limited number of patients and possible biased selection of cases who demonstrating severe hyperthyroidism. Our data in this study are similar to those of Krassas et al. [7], although they could not find any cases of amenorrhea. We found amenorrhea in 0.9% of 586 patients with Graves’ hyperthyroidism. Interestingly, this prevalence was increased to 2.5% among severe cases (FT3 30 pg/mL or more) and amenorrhea is 10 times more frequent in severe cases compared to that in mild or moderate cases (0.2%). When the severity of disease was stratified by serum FT4 levels, we could not demonstrate a significant difference. FT3 may be more directly related to the pathological state in Graves’ disease.

Painless or silent thyroiditis shows destructive transient thyrotoxicosis, usually within a 3 month duration, in the early stage of disease [11, 12]. The concept of this disease was newly established around 30 years ago [11], and there are no data on menstrual disturbances in this disease. Hence, we investigated this point. As expected, there was no significant increase in frequency of menstrual disturbances in painless thyroiditis. It is possible that the short duration of thyrotoxicosis would not influence the menstrual disturbances.

In hypothyroidism, high frequency of menstrual disturbances has also been emphasized for a long time. In 1952, Goldsmith et al. [2] examined 10 patients with myxedema and menstrual disturbances were found in 80% of them. In 1955, Benson et al. [3] also found high frequency of hypermenorrhea or polymenorrhea: 18 (58%) of 31 patients with hypothyroidism who developed hypothyroidism after treatment of hyperthyroidism. In 1964, Scott et al. [4] examined 50 patients with

<table>
<thead>
<tr>
<th>TSH (μIU/mL)</th>
<th>Less than 100 (%)</th>
<th>100 and more (%)</th>
<th>Healthy controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary amenorrhea</td>
<td>0 (0)</td>
<td>2 (8.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypomenorrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>4 (4.5)</td>
<td>2 (8.7)</td>
<td>14 (13.3)</td>
</tr>
<tr>
<td>Hypermenorrhea</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>0 (0)</td>
<td>2 (8.7)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Irregular menstrual cycle</td>
<td>5 (5.7)</td>
<td>2 (8.7)</td>
<td>7 (6.7)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (10.2)</td>
<td>8 (34.8)*</td>
<td>25 (23.8)</td>
</tr>
</tbody>
</table>

Data indicate numbers of patients and numbers in parentheses indicate percentages. * Significantly high at $p<0.01$ compared to the group showing a TSH level less than 100.
myxedema and found 2 cases (4%) of amenorrhea, and furthermore, 23 cases (46%) with menorrhagia, metrorrhagia or monometrorrhagia. Totally 60% of them had menstrual disturbances. In 1993, Joshi et al. [10] examined 22 patients with hypothyroidism and found 8 cases (36.4%) of hypomenorrhea /oligomenorrhea and 5 cases (22.7%) of hypermenorrhea /polymenorrhea. In 1999, Krassas et al. [8] examined 171 patients with hypothyroidism and found higher frequencies of amenorrhea (5 cases, 2.9%) and hypermenorrhea (12 cases, 7.0%) than those among normal controls. In their study, oligomenorrhea was found in 9.9% and this was higher than that (5.3%) in patients with hyperthyroidism.

Our findings among patients with hypothyroidism are similar to those of Krassas et al. [8]. In an earlier study, they observed mainly patients with myxedema, which is a severe stage of hypothyroidism. Thus, the reported high frequency of menstrual disturbances may not be generalized to ordinary patients with hypothyroidism. Regarding this, we divided our patients into two groups, mild/moderate and severe cases based on the serum levels of TSH. The severe group had a higher frequency of menstrual disturbances (34.8%) than the mild/moderate group (10.2%), suggesting that disease severity markedly influences menstrual disturbances.

It is well known that thyroid dysfunction not only influences menstrual disturbances but also affects reproductive activity, fertility and pregnancy outcome [5, 13]. Even though the thyroid function is normal, the presence of anti-thyroid antibodies is related to a high frequency of miscarriage [13, 14]. It is suggested that thyroid autoimmunity itself also influences female reproductive activity. Consequently, it is necessary to clarify the prevalence of menstrual disturbances in euthyroid patients with chronic thyroiditis. However, in our review of the literature, there are no data on issue. In this study, we examined 558 euthyroid patients with chronic thyroiditis but there was no difference in the prevalence of menstrual disturbances between patients and normal controls. To clarify the suitability of the protocol of this study, we further examined patients with thyroid tumor as patient controls and there were no significant abnormalities.

In conclusion, the prevalence of menstrual disturbances, including secondary amenorrhea, hypomenorrhea, oligomenorrhea, hypermenorrhea, polymenorrhea and irregular menstrual cycle, in patients with various thyroid diseases, such as hyperthyroidism, hypothyroidism, euthyroid patients with chronic thyroiditis, painless thyroiditis and thyroid tumor, did not differ from that in healthy controls. However, patients with severe hyperthyroidism had a higher prevalence of secondary amenorrhea and hypomenorrhea than those with mild or moderate disease. Moreover, patients with severe hypothyroidism had a higher prevalence of menstrual disturbances than mild/moderate cases. Menstrual disturbances in thyroid dysfunction were less frequent than previously thought.

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References