Post-partum and non-post-partum relapsing Graves' hyperthyroidism display different response to anti-thyroid drugs

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Abstract

Design: Graves' disease (GD) patients in remission after a full course of methimazole (MMI) therapy are at risk for a relapse of hyperthyroidism during the post-partum (PP) period, but whether this relapse may display any peculiarity is still unknown. Aim of this study was to compare GD patients undergoing a relapse of hyperthyroidism either in the PP period or not.

Methods: We retrospectively evaluated forty-three GD female patients in their childbearing age who experienced a relapse of hyperthyroidism. Eighteen of them relapsed in the PP period (i.e. within 12 months after delivery, PP group); the remaining 25 relapsed elsewhere during life (NPP group).

Results: Age at relapse, thyroid volume, thyroid function tests, TRAb titers, smoking habit, presence and degree of orbitopathy and duration of methimazole (MMI) treatment did not differ in the two groups. However, the remission rate was much greater (79%) in the PP as compared with the NPP (32%) group ($P=0.002$). A significant reduction in TRAb levels occurred at 12-month MMI treatment in the PP ($F=9.016$; $P=0.001$), but not in the NPP group ($F=2.433$; NS). At 12 months, the PP group had significantly lower mean TRAb levels (0.6 ± 1.1 U/L and 4.5 ± 4.7 U/L in the PP and the NPP group, respectively; $P=0.029$).

Conclusions: Relapsing Graves' hyperthyroidism in the PP period is more prone to undergo a remission after a second course of MMI treatment. In these patients, a conservative therapeutic approach is more appropriate.

European Journal of
Endocrinology
(2018) 178, 589–594

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in iodine-sufficient areas (1). Anti-thyroid drugs (ATD), namely thionamides (methimazole (MMI), carbimazole (CBZ), and propylthiouracil (PTU)) (2, 3), represent the first-line therapy for Graves' hyperthyroidism (2, 4). Apart from the rare side effects of thionamides, the major problem with medical treatment of Graves' hyperthyroidism is the high relapse rate after

ATD withdrawal (2, 4, 5). Besides the genetic background, several factors including male gender, younger age, large goiter, smoking habit, presence of active/severe orbitopathy and elevated serum TSH-receptor antibodies (TRAb) at presentation were identified as predictors of relapsing hyperthyroidism after ATD withdrawal (6, 7, 8). Although two recent reports, as well as an extensive literature review suggest that relapsing Graves'

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hyperthyroidism can be successfully treated with a second course of ATD (7, 9, 10), it is commonly believed that, once hyperthyroidism recurs after ATD withdrawal, there is little chance of inducing a permanent remission with thionamide therapy. Thus, definitive treatment of hyperthyroidism, either with radioiodine (RAI) or with thyroidectomy, is often advised (2). Both therapeutic strategies, although effective in curing hyperthyroidism, produce permanent hypothyroidism with subsequent need of lifelong levothyroxine (LT4) replacement (2).

The PP, which comprises the 12-month period after delivery, is typically characterized by an exacerbation of autoimmune thyroid diseases (11, 12, 13). The reason for this is a rebound activation of the immune system, which follows the physiologic immune deviation of pregnancy aimed at minimizing the maternal cell-mediated immune response against the fetus (3, 8). Immune changes in the PP period are mainly characterized by a Th2 to Th1 return shift, which accounts for the aggravation not only of ATD, but also of other Th1-dependent autoimmune disease, such as rheumatoid arthritis (11, 14, 15, 16). In a previous study, we demonstrated that female GD patients being in remission after a full course of MMI therapy are particularly at risk for relapsing hyperthyroidism during the PP period (17). To the best of our knowledge, no study so far evaluated the clinical phenotype of relapsing Graves' hyperthyroidism in the PP period, neither its outcome after medical therapy. This topic was investigated in the present study by comparing two groups of female GD patients undergoing a relapse of hyperthyroidism after an apparently successful course of MMI treatment. In the first group of patients (cases), hyperthyroidism relapsed in the PP period, while in the second group of patients (controls), hyperthyroidism recurred elsewhere during life.

Subjects and methods

Patients

We searched the outpatients' Database of the Unit of Internal Medicine and Endocrinology of ICS Maugeri Hospital (Pavia, Italy) for consecutive female patients with GD experiencing a relapse of hyperthyroidism after a period of euthyroidism, which lasted at least 12 months, after completion of a full course (minimum 12 months) of MMI treatment. Inclusion criteria were (1) patients who experienced GD in the childbearing

age, as defined by an age at diagnosis ranging from 20 to 45 years; (2) availability of a reproductive history, including the number of full term pregnancies after the diagnosis of GD, (3) availability of a complete thyroid work-up, which included serum TSH, FT4, FT3 and TRAb measurements, and thyroid ultrasound at the time of relapsing Graves' hyperthyroidism. In our institution, the therapeutic choice in the presence of relapsing Graves' hyperthyroidism encompasses two strategies: (1) destructive thyroid therapy (either with radioiodine ablation or thyroidectomy); (2) a second course of MMI treatment. The latter strategy is advised to patients meeting specific criteria: (1) absence of large goiter; (2) absence of active and/or severe Graves' orbitopathy; (3) no previously experienced ATD-related side effects and (4) good compliance to previous ATD treatment. For the purpose of this study, good compliance to ATD treatment was defined when: (1) patients attended regular follow-up visit; (2) lack of self-made adjustments and/or stopping ATD assumption. Patients who in spite of not fulfilling all the previously mentioned criteria, refused destructive thyroid treatment by choosing a second ATD course were excluded from the present study.

A total of 43 patients fulfilled all the inclusion criteria and were included in the study. All patients were Caucasians and lived in Pavia or in the surrounding region, an area characterized by mild iodine deficiency. They were started on MMI for relapsing Graves' hyperthyroidism and regularly attended the outpatient endocrine consultations both during ATD treatment and for at least 12 months after ATD withdrawal. Relapsing hyperthyroidism was diagnosed in the presence of low serum TSH and high free thyroid hormone levels associated with positive TRAb tests. An ultrasound scan of the thyroid gland was performed in all patients and was consistent with a diagnosis of GD, including evidence of an increased thyroid blood flow.

Patients were stratified in two groups according to the time of relapsing Graves' hyperthyroidism: PP- (cases) and non-PP- (controls) related recurrence. Relapsing hyperthyroidism being diagnosed within 12 months after delivery was considered to be a PP-related recurrence. The median (range) time after delivery when hyperthyroidism relapsed was 5 months (2, 3, 4, 5, 6, 7, 8, 9, 10). Relapsing hyperthyroidism occurring later than 12 months after delivery or in women with no history of pregnancy was considered as a non-PP-related recurrence.

The PP-related recurring (PP) group included 18 women, while 25 patients constituted the non-PP (NPP)-related recurrence group. Patients in both groups were

addressed to a second course of MMI treatment. ATD failure was defined when patients experienced further episodes of relapsing hyperthyroidism either during or after MMI treatment. In all patients, the dose of MMI throughout treatment was adjusted by the back-titration method. Remission of GD was defined as clinical and biochemical euthyroidism lasting at least 12 months after withdrawing ATD, associated with negative tests for circulating TRAb.

All patients signed an informed consent concerning the future use of their clinical-pathological data for research purposes. This study was approved by the institution ethics reviewing board on human experimentation.

Laboratory assays

The serum concentrations of TSH (third-generation TSH assay; normal range: 0.4–4 mIU/L), FT3 (normal range: 1.8–4.2 pg/mL) and FT4 (normal range: 0.89–1.76 ng/mL) were measured using an immune-chemiluminescent assay run by an automated analyzer (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA) employing commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The sensitivity of the assay was 0.004 mIU/L, 1.0 pg/mL and 0.3 ng/dL for TSH, FT3 and FT4, respectively. TRAb was measured by radioreceptor assay (LIA TRAK human; Brahms, Hennigsdorf, Germany). The sensitivity was 1.0 U/L.

Statistical analysis

Statistical analysis was performed using SPSS software. Mean group values were compared by using one-way ANOVA for normally distributed variables. *Post hoc* analysis was performed according to the Bonferroni's

correction for multiple comparisons. Between-group comparisons were performed by means of Student *t* test for unpaired data and Mann–Whitney *U* test according to a normal or a nonparametric distribution of the variable tested. Frequencies among groups were compared by χ^2 test with Fisher's correction, when appropriate. $P < 0.05$ was considered statistically significant.

Results

First diagnosis of Graves' disease

Patients belonging to the PP and NPP groups received the first diagnosis of GD at a similar mean age (31.4 ± 6.1 years and 32.6 ± 6.1 years, $P = 0.56$; in the PP and in the NPP group, respectively). They also experienced a similar duration of remission after the first course of MMI therapy (15.9 ± 9.9 months and 21.8 ± 19.9 months $P = 0.27$; in the PP and in the NPP group, respectively).

Relapse of Graves' hyperthyroidism

Table 1 shows the clinical and demographic characteristics of patients in the PP and the NPP group at the time of relapsing hyperthyroidism. Known risk factors for a more aggressive GD (age, thyroid volume, Graves' orbitopathy (which however was always mild non-active), smoking habit, serum levels of free thyroid hormones and TRAb) did not significantly differ between the two groups (Table 1). The starting dose of MMI did not differ in the two groups (20.3 ± 8.0 mg/day and 20.6 ± 9.01 mg/day $P = 0.9$; in the PP and in the NPP group, respectively).

The outcome of medical treatment significantly differed between the two groups (Fig. 1), because the

Table 1 Clinical and biochemical characteristics of Graves' patients experiencing relapsing hyperthyroidism stratified according to the PP or the NPP occurrence.

	PP group (n = 18)	NPP group (n = 25)	P value
Age at recurrence (years)	34.4 ± 6.0	36.9 ± 5.7	NS
Mild non-active Graves' orbitopathy (yes/no)	1/17	3/22	NS
Smoking habit (yes/no)	4*/14	1/24	NS
TSH (mIU/L) [§]	0.02 ± 0.07	0.01 ± 0.01	NS
FT4 (ng/mL) [§]	2.78 ± 1.17	2.67 ± 1.16	NS
FT3 (pg/mL) [§]	7.64 ± 4.05	8.07 ± 3.67	NS
TRAb (U/L) [§]	4.37 ± 2.95	7.25 ± 7.22	NS
Thyroid volume (mL) [§]	17.4 ± 6.9	17.4 ± 6.1	NS
Starting MMI dose (mg/day)	20.3 ± 8.0	20.6 ± 9.1	NS

*All patients stopped smoking throughout pregnancy and 1 of them restarted smoking 2 months post-partum; [§]at diagnosis of relapsing hyperthyroidism.

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Figure 1

Outcome of medical treatment of relapsing Graves' hyperthyroidism in the PP and NPP group. A significantly ($P=0.002$) higher rate remission after MMI treatment characterizes the PP group as compared to the NPP group.

remission rate was 79% in the PP group as compared with 32% in the NPP group ($P=0.002$). Accordingly, the lowest MMI dose able to maintain euthyroidism was lower in the PP group as compared to the NPP group (3.9 ± 3.3 vs 6.7 ± 4.1 mg/day, in the PP and in the NPP group, respectively; $P=0.046$). This issue was further addressed by analyzing the lowest MMI dose, which was able to maintain euthyroidism in the PP as compared with the NPP group after stratification according to success or failure of ATD treatment. No significant difference in the mean effective MMI dose was found in patients achieving remission (3.0 ± 1.1 vs 3.1 ± 1.2 mg/day, in the PP and in the NPP group, respectively; $P=0.921$). Similar results were found in patients experiencing ATD failure (5.5 ± 5.4 vs 7.6 ± 4.1 mg/day, in the PP and in the NPP group, respectively; $P=0.353$). Moreover, patients experiencing remission or failure after ATD did not differ for the number of pregnancies (1.31 ± 0.94 and 0.87 ± 0.94 for remission and failure, respectively; $P=0.137$).

During MMI treatment, the serum levels of TRAb behaved differently in the two groups of patients. As shown in Fig. 2, separate ANOVA analysis demonstrated a significant reduction in TRAb levels in the PP ($F: 9.016$; $P=0.001$), but not in the NPP ($F: 2.433$; NS) group. After 12 months of MMI treatment, patients in the PP group showed significantly lower mean TRAb levels compared with those in the NPP group (0.6 ± 1.1 U/L and 4.5 ± 4.7 U/L, in the PP and in the NPP group, respectively; $P=0.029$).

Figure 2

Changes of serum TRAb levels during MMI treatment for relapsing Graves' hyperthyroidism in the PP and in the NPP group. Data expressed as mean $\pm$ s.d. *Student *t* test for unpaired data (PP vs NPP) at baseline, 6 and 12 months of MMI treatment; § ANOVA for NPP group; § ANOVA and Bonferroni's correction for PP group.

Discussion

The results of this study show that the success rate of a second course of MMI treatment in childbearing age women who experienced a relapse of Graves' hyperthyroidism is strikingly higher when the relapse occurs in the PP period as compared to the NPP. Evidence for this finding is particularly strong because in the present study, the two groups of patients with relapsing Graves' hyperthyroidism did not differ for factors associated with a poor outcome of ATD treatment, such as age, thyroid volume, smoking habit, presence of orbitopathy and serum TSH, FT4, FT3 and TRAb levels at presentation. Thus, the severity of relapsing hyperthyroidism was similar in the PP as compared with NPP group of patients.

The starting dose of MMI did not significantly differ between the PP and NPP group, while the lowest dose of MMI able to maintain euthyroidism was significantly higher in the NPP group. In view of the higher rate of patients experiencing MMI failure, this finding could be expected in the NPP group. Stratification of patients in relation to success/failure of ATD revealed that the lowest MMI dose able to maintain euthyroidism did not differ between patients in the PP and NPP groups.

The most likely explanation accounting for the different remission rates after MMI treatment in the PP as compared with the NPP group of relapsing GD patients resides in the peculiar immunologic setting of the PP period, which is characterized by an aggravation of autoimmune diseases (11). This concept particularly relates to Th1-immuno-oriented conditions, such as

rheumatoid arthritis, multiple sclerosis and autoimmune thyroid diseases (18, 19). After delivery, a transient immunologic rebound occurs, which includes a Th2 to Th1 return shift (11) and a dysregulation of Treg cells (19). The rebound phase may last up to 12 months after delivery and is followed by a restoration of the pre-pregnancy immune balance (19). This restoration phase may synergize with the immune modulating effects of MMI, which result in a reduction of circulating thyroid antibodies and in a decrease of intrathyroidal lymphocytic infiltration (20, 21, 22, 23). In this scenario, it is reasonable to believe that the progressive attenuation of the PP immune rebound, which occurs later after delivery, plays an important role in favoring the remission of hyperthyroidism after ATD treatment (19). This immune advantage would result in a higher remission rate.

Our hypothesis is supported by the different behavior of circulating TRAb, which, after 12 months of MMI treatment, were found to be significantly lower in the PP as compared with the NPP group of relapsing GD patients. Because negative tests for TRAb at the time of ATD withdrawal can predict a sustained remission of Graves' hyperthyroidism (7, 24), it is not surprising that medical treatment was much more successful in the PP as compared with the NPP group of hyperthyroid patients.

In conclusion, the results of the present study demonstrate that the biochemical phenotype of relapsing Graves' hyperthyroidism occurring in the PP and NPP period is superimposable as assessed by TRAb and thyroid function parameters at diagnosis. However, the response to ATD treatment profoundly differs between the two groups, because patients with a PP relapse have a significantly higher chance of achieving remission after a second course of MMI. Our findings have relevant clinical implications because they indicate that a conservative therapeutic approach is more appropriate in GD patients experiencing a relapse of hyperthyroidism in the PP period.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 27 December 2017

Revised version received 2 March 2018

Accepted 20 March 2018