The Effect of Pregnancy on Subsequent Relapse from Graves' Disease after a Successful Course of Antithyroid Drug Therapy

Mario Rotondi, Carlo Cappelli, Barbara Pirali, Ilenia Pirola, Flavia Magri, Rodolfo Fonte, Maurizio Castellano, Enrico Agabiti Rosei, and Luca Chiovato

Unit of Internal Medicine and Endocrinology (M.R., B.P., F.M., R.F., L.C.), Fondazione Salvatore Maugeri Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Superiore Prevenzione e Sicurezza Lavoro Laboratory for Endocrine Disruptors, University of Pavia, I-27100 Pavia, Italy; and Department of Medical and Surgical Sciences (C.C., I.P., M.C., E.A.R.), Internal Medicine and Endocrinology Unit, University of Brescia, I-25100 Brescia, Italy

Objective: Pregnancy and the postpartum (PP) period are associated with profound changes of the immune system, which largely influence the clinical activity of autoimmune diseases. The aim of this study was to evaluate the effect of pregnancy and/or the PP period in driving a clinical relapse of hyperthyroidism in patients with Graves' disease (GD) who are in remission after antithyroid drug (ATD) treatment. Data were retrospectively collected from 150 female patients with GD, who were assigned to two groups according to the occurrence of a successful pregnancy after ATD withdrawal.

Results: Relapsing Graves' hyperthyroidism was observed in 70 of 125 patients in group I (no pregnancy after ATD withdrawal) (56.0%) and 21 of 25 patients in group II (pregnancy after ATD withdrawal) (84.0%) ($P < 0.05$). Logistic regression analysis (dependent variable: relapse/nonrelapse; covariates: age, positive family history for autoimmune thyroid disease, duration of treatment with ATD, number pregnancies at diagnosis, number of pregnancies after ATD withdrawal) showed a significant effect only for the number of pregnancies after ATD withdrawal [4.257 (1.315–13.782)]. The effect was ascribed to the PP period rather than to pregnancy itself because in 20 of 21 patients of group II (95.2%), the relapse of Graves' hyperthyroidism occurred between 4 and 8 months after delivery.

Conclusions: The PP period is significantly associated with a relapse of hyperthyroidism in GD patients being in remission after ATD. We therefore recommend that patients with GD in remission after a course of ATD should have their thyroid function tested at 3 and 6 months after delivery. (***J Clin Endocrinol Metab*** **93: 3985–3988, 2008)**

Graves' disease (GD) is aggravated in early pregnancy, ameliorates in the second half of gestation, and often reexacerbates in the postpartum (PP) (1–3). Studies aimed at identifying possible predictive factors for the PP aggravation of Graves' hyperthyroidism showed that, among all GD patients undergoing pregnancy, those experiencing a thyrotoxic phase in early pregnancy are at higher risk of developing severe hyperthyroidism in the PP period (2). The medical treatment of Graves' hyperthyroidism with thionamides (methimazole or propylthiouracile), although effective in reestablishing euthyroidism, is associated with a high rate of relapsing hyperthyroidism once these drugs are discontinued (4, 5). In the majority of cases, relapses of hyperthyroidism occur between 6 months and 2 yr after discontinuation of antithyroid drugs (ATD), but long-term relapses may also occur after this period (4). Despite these discouraging results, a consistent percentage (nearly 30%) of Graves' patients will enter a prolonged remission after ATD. Thus, medical treatment still remains a valid therapeutic option in GD (1, 3).

Abbreviations: AITD, Autoimmune thyroid disease; ATD, antithyroid drug; GD, Graves' disease; MMI, methimazole; PP, postpartum.

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2008-0966 Received May 5, 2008. Accepted July 21, 2008.

First Published Online July 29, 2008

Normal pregnancy is associated with profound changes of the immune system, which largely influence the clinical activity of autoimmune diseases (6–8). It is known that during pregnancy a shift to a type 2 polarized cytokine profile occurs, which minimizes the maternal cell-mediated immune response against the fetus (7). These changes allow maintaining the fetal-maternal allograft, which is not rejected despite diverse paternal histocompatibility antigens (9). These pregnancy-induced changes result in a down-regulation of the Th1-mediated effector arms of the immune system, which sustain the clinical remission observed during pregnancy in most patients with autoimmune thyroid disease (AITD) (7). On the other hand, the PP period is characterized by a rebound reaction which, accounts for the aggravation of AITD during the puerperium (10, 11). The PP-rebound immunity, which is characterized by a Th2 to Th1 return shift, is considered to be responsible for the reactivation of not only AITD but also other Th1-dependent autoimmune disease, such as rheumatoid arthritis (12–15).

The role played by the PP-rebound of immunity, on both the *de novo* occurrence of GD and the clinical course of GD in patients treated with ATD, have been previously investigated (16–18). However, little is known on the effect played by pregnancy and the PP period in patients with GD, who are in remission after ATD.

The aim of this study was to evaluate the effect of pregnancy and/or the PP period in driving a clinical relapse of hyperthyroidism in GD patients who were in remission after ATD.

Patients and Methods

Patients

The study group encompassed female patients who received a diagnosis of GD in our outpatient clinics between 2000 and 2005. Inclusion criteria were: 1) female patients experiencing GD in their child-bearing age; 2) availability of a reproductive history, including the number of full-term pregnancies before the diagnosis of GD and throughout the study span; 3) completion of a full course (at least 12 months) of methimazole (MMI) treatment with restoration of euthyroidism, as assessed by normal serum levels of free T_4, free T_3, and TSH; and 4) remission of Graves' hyperthyroidism, as assessed by clinical and biochemical euthyroidism, lasting for at least 6 months after withdrawing ATD.

A total number of 214 GD patients fulfilled the above criteria. All patients were Caucasians. Their median age and range was 32 (19–43) yr. Hyperthyroid GD and relapsing Graves' hyperthyroidism were diagnosed by measuring the serum concentrations of free T_4, free T_3, and TSH and searching for circulating thyroid antibodies (antithyroglobulin, antithyroperoxidase, and anti-TSH receptors antibodies). 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. Thyroid scintiscan was performed in doubt cases to rule out destructive thyroiditis. The child-bearing age was defined, taking into account the age of the youngest (19 yr) and oldest (43 yr) woman with GD, who experienced a successful pregnancy. The PP period was defined as 1 yr after delivery. To evaluate the role of pregnancy and the PP period in precipitating a relapse of hyperthyroidism, two groups of patients were constituted: group I encompassed 189 patients, who did not undergo pregnancy after stopping MMI treatment. Group II encompassed 25 patients, who had at least one successful pregnancy after stopping MMI. The mean age was significantly greater ($P = 0.0001$) in group I (32.1 ± 5.3 yr), compared with group II (27.3 ± 5.8 yr). To balance the two groups for the age factor, patients in group I were stratified according to their age at diagnosis and, starting from the oldest one, they were excluded from the study until a nonsignificant difference was reached for the mean age between patients in groups I and II. After this procedure, the final group I encompassed 125 patients with GD who did not have a pregnancy after stopping MMI treatment. GD patients were treated with ATD for a median time of 17.5 (12–120) months. The length of the surveillance period, including patients who experienced a relapse of hyperthyroidism, was 16 (6–360) months.

Informed consent, concerning the future use of clinical-pathological data for research purposes, is routinely obtained from all patients attending our clinics. This study was in accordance with the Institution Ethics Committee on human experimentation.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL). 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. To test the effects of different variables independently of a covariate, binary logistic regression analysis was used and partial correlation coefficients were computed. $P < 0.05$ was considered statistically significant.

Results

Clinical data of patients with GD, subdivided into two groups according to the occurrence of a pregnancy during the follow-up period, are shown in Table 1. In detail, the two groups did not significantly differ in age, duration of treatment with MMI, and total follow-up time. A significantly shorter time to relapse after ATD withdrawal characterized women in group I.

As shown in Fig. 1, a statistically significant difference for the relapse rate between patients in groups I and II was observed. Indeed, a relapse of Graves' hyperthyroidism was observed in 70 of 125 patients in group I (56.0%) and 21 of 25 patients in group II (84.0%; $P < 0.05$).

To further evaluate the effect of pregnancy in precipitating a relapse of hyperthyroidism in GD patients being euthyroid after ATD, multiple regression analysis was used. A logistic regression model was constructed by entering the relapse/nonrelapse as the dependent dichotomic variable, whereas age, positive family history for AITD, duration of treatment with ATD, number of pregnancies at diagnosis, and number of pregnancies after ATD withdrawal were entered as covariates. The results shown in Table 2

TABLE 1. Clinical data of GD patients according to the occurrence of a pregnancy after ATD withdrawal

	Group I	Group II	*P* value
Number of cases	125	25	
Age (yr)	29 (19–35)	27 (21–40)	NS
Duration of MMI treatment (months)	18 (12–120)	16 (12–36)	NS
Total follow-up (months)	16 (6–360)	19 (12–62)	NS
Time to relapse after MMI withdrawal (months)	**14 (6–144)**	**19 (12–62)**	**<0.0001**
Time to relapse after delivery (months)		6 (4–24)	

Significant variables are in *bold* characters. NS, Not significant.

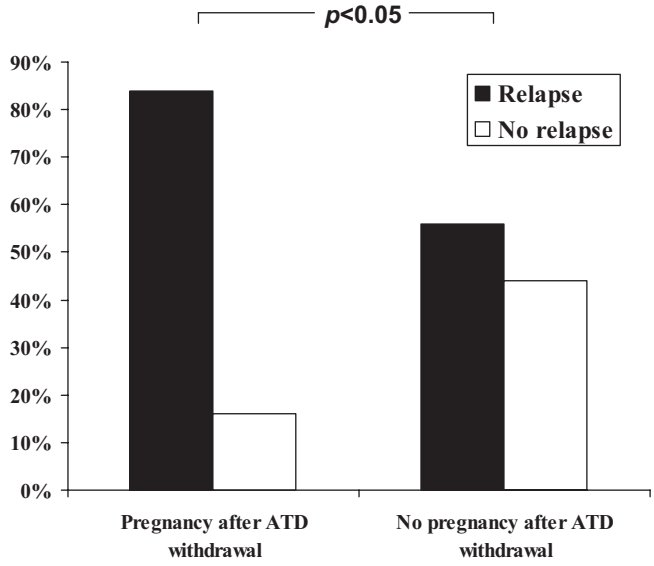

FIG. 1. Relapsing Graves' hyperthyroidism was observed in 21 of 25 patients who had a pregnancy after ATD withdrawal (84.0%) and 70 of 125 patients who did not become pregnant since ATD withdrawal (56.0%) (λ^2 and Fisher's exact test; $P < 0.05$).

indicate that only the number of pregnancies after ATD withdrawal was significantly related to the occurrence of relapsing hyperthyroidism. The specificity of this finding was confirmed by the lack of any significant effect of the number of pregnancies at the first diagnosis of GD. To discriminate the role of pregnancy and the PP period as a risk factor for relapsing hyperthyroidism, the timing of the relapse was further evaluated in patients of group II. None of these patients experienced a relapse of hyperthyroidism during gestation. In 20 of 21 patients (95.2%), a relapse of Graves' hyperthyroidism occurred in the PP period (between 4 and 8 months after delivery). In only one of 21 women (4.8%), relapsing hyperthyroidism occurred after the PP period (24 months after delivery). In only four of 59 patients who remained in remission throughout the study span (6.8%), a pregnancy was recorded after MMI withdrawal.

Discussion

In our series of female patients with GD, the overall relapse rate of hyperthyroidism after ATD treatment was 60.1%. A significantly higher rate of relapsing hyperthyroidism was found in patients who underwent a pregnancy after stopping ATD, as opposed to patients who did not become pregnant. It is important to note that in none of these patients, relapsing hyperthyroidism occurred during the first trimester of gestation. By contrast, in more than 95% of women who became pregnant after ATD withdrawal and experienced a relapse of GD, hyperthyroidism developed in the PP period. Furthermore, no significant association between the number of successful pregnancies at diagnosis of GD and the occurrence of relapsing hyperthyroidism after ATD was found by multiple regression analysis. Taken together, these findings indicate that the PP period, rather than pregnancy itself, plays a major role in promoting a relapse of hyperthyroidism in GD patients being in remission after ATD treatment.

TABLE 2. Relative risks for relapsing Graves' hyperthyroidism after ATD withdrawal

	P value	Relative risk	95% CI	
			Lower	Upper
Age (yr)	0.442	1.038	0.944	1.140
Positive family history for AITD	0.187	0.606	0.289	1.274
Duration of MMI treatment (months)	0.360	1.022	0.976	1.070
Pregnancies after ATD withdrawal	**0.016**	**4.257**	**1.315**	**13.782**
Number of pregnancies at diagnosis of GD	0.710	0.908	0.545	1.511

Significant variables are in *bold* characters. CI, Confidence interval.

The fact that the PP period, rather than pregnancy itself, favors the relapse of Graves' hyperthyroidism makes sense according to our current knowledge of the changes in the immune system associated with the PP period, which have been described in the introductory text.

The design of the current study has some limitations because it was a retrospective one, whereas a prospective longitudinal study would be more appropriate for assessing the impact of pregnancy on the relapse of Graves' hyperthyroidism in patients successfully treated by ATD. In the current study, the influence of age at diagnosis of GD, which was previously reported to be negatively related to a worse outcome after ATD treatment (19, 20), was tested using a multivariate logistic regression model. This analysis showed a nonsignificant influence of the age factor on relapsing Graves' hyperthyroidism. However, a case-control study with an age-matching criterion between patients with and without a successful pregnancy after ATD withdrawal would be helpful to further rule out the effect of age. Thyroid volume, serum levels of free thyroid hormones, and titers of anti-TSH receptor antibodies, previously reported to influence the rate of successful ATD treatment (5, 19), were not taken into account in the present study.

Two clinical recommendations stem from our findings. First, thyroid function should be carefully monitored in female patients with GD who undergo a pregnancy while being in remission after ATD treatment. This would be in line with the most recently published guidelines on the treatment of thyroid dysfunction in pregnancy, which suggest evaluating thyroid function at 3 and 6 months after delivery in those women who are at risk for postpartum thyroiditis (2). On the basis of our results, it seems reasonable to behave similarly in Graves' patients by evaluating serum thyroid function parameters and anti-TSH receptors antibodies at 3 and 6 months after delivery. Second, definitive treatment with thyroidectomy or radioiodine should be strongly considered in female patients with GD who plan to become pregnant in the following years.

In conclusion, these results indicate that the PP period is significantly associated with a relapse of hyperthyroidism in GD patients being in remission after ATD. We therefore recommend that patients with GD in remission after a course of ATD should have their thyroid function tested at 3 and 6 months after delivery.

Acknowledgments

Address all correspondence and requests for reprints to: Luca Chiovato, M.D., Ph.D., Unit of Internal Medicine and Endocrinology, Fondazione Salvatore Maugeri Istituto di Ricovero e Cura a Carattere Scientifico Chair of Endocrinology, University of Pavia, Via S. Maugeri 10, I-27100, Pavia, Italy. E-mail: luca.chiovato@fsm.it.

The experiments reported in this paper were supported in part by the Progetto di Ricerca Finalizzata ex art. 12, del D.Lgs.502/92-2005.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Cooper DS** 2005 Antithyroid drugs. N Engl J Med 352:905–917
2. **Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A** 2007 Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 92:S1–S47
3. **Brent GA** 2008 Clinical practice. Graves' disease. N Engl J Med 358:2594–2605
4. **Marinò M, Chiovato L, Pinchera A** 2006 Graves' disease. In: De Groot LJ, Jameson Saunders JL, eds. Endocrinology. Philadelphia: Elsevier Saunders; 1995–2028
5. **Glinoer D, de Nayer P, Bex M** 2001 Effects of L-thyroxine administration, TSH-receptor antibodies and smoking on the risk of recurrence in Graves' hyperthyroidism treated with antithyroid drugs: a double-blind prospective randomized study. Eur J Endocrinol 144:475–483
6. **Weetman AP** 1999 The immunology of pregnancy. Thyroid 9:643–646
7. **Aagaard-Tillery KM, Silver R, Dalton J** 2006 Immunology of normal pregnancy. Semin Fetal Neonatal Med 11:279–295
8. **Formby B** 1995 Immunologic response in pregnancy. Its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. Endocrinol Metab Clin North Am 24:187–205
9. **Moffett A, Loke YW** 2004 The immunological paradox of pregnancy: a reappraisal. Placenta 25:1–8
10. **Davies TF** 1999 The thyroid immunology of the postpartum period. Thyroid 9:675–684
11. **Amino N, Tada H, Hidaka Y** 1999 Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. Thyroid 9:705–713
12. **Muller AF, Drexhage HA, Berghout A** 2001 Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care. Endocr Rev 22:605–630
13. **Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR** 2006 Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid 16:573–582
14. **Rotondi M, Chiovato L, Romagnani S, Serio M, Romagnani P** 2007 Role of chemokines in endocrine autoimmune diseases. Endocr Rev 28:492–520
15. **Hammoudeh M** 2006 Recurrent postpartum episodic rheumatoid arthritis. J Clin Rheumatol 12:196–198
16. **Rochester DB, Davies TF** 2005 Increased risk of Graves' disease after pregnancy. Thyroid 11:1287–1290
17. **Nakagawa Y, Mori K, Hoshikawa S, Yamamoto M, Ito S, Yoshida K** 2002 Postpartum recurrence of Graves' hyperthyroidism can be prevented by the continuation of antithyroid drugs during pregnancy. Clin Endocrinol (Oxf) 57:467–471
18. **Tagami T, Hagiwara H, Kimura T, Usui T, Shimatsu A, Naruse M** 2007 The incidence of gestational hyperthyroidism and postpartum thyroiditis in treated patients with Graves' disease. Thyroid 17:767–772
19. **Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, Rocchi R, Martino E, Pinchera A** 1997 Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid 7:369–375
20. **Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA** 2000 Age and gender predict the outcome of treatment for Graves' hyperthyroidism. J Clin Endocrinol Metab 85:1038–1042