Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of recurrent hyperthyroidism developing during the postpartum period

Rotondi M, Cappelli C, Pirali B, Pirola I, Magri F, Fonte R, Castellano M, Rosei EA, Chiovato L. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. J Clin Endocrinol Metab 2008;93:3985-8.

SUMMARY

BACKGROUND Pregnancy and the postpartum (PP) period induce major changes in the immune system that influence the clinical activity of autoimmune diseases. The aim of this study was to evaluate the effect of the PP period on the relapse of hyperthyroidism in patients with Graves' disease who were in remission after the withdrawal of antithyroid drug treatment (ATD).

METHODS This is a retrospective study of 150 women with Graves' disease. All had completed a full course of at least 12 months of methimazole (MMI) therapy with restoration of euthyroidism lasting for at least 6 months after ATD withdrawal. To evaluate the role of pregnancy and the PP period, patients were divided into two groups: those in group 1 did not become pregnant after stopping MMI, and patients in group 2 had at least one successful pregnancy after stopping MMI.

RESULTS A total of 214 women with Graves' disease fulfilled the study criteria. All were white. Their median age was 32 years (range, 19 to 43). There were 189 patients in group 1 and 25 in group 2. Because the mean (±SD) age was significantly greater in group 1 (32.1±5.3) than in group 2 (27.3±5.8) (P = 0.001), the patients in group 1 were stratified according to their age at diagnosis and, starting from the oldest patient, were excluded from the study until there were no significant differences in the mean ages of the two groups. After this adjustment, there were 125 patients with Graves' disease in group 1 who did not become pregnant after stopping MMI for a median of 17.5 months (range, 12 to 120). The length of follow-up was 16 months (range, 6 to 360), including the patients who experienced a relapse of hyperthyroidism. The two groups did not differ significantly in age, duration of MMI therapy, and follow-up. The relapse rate

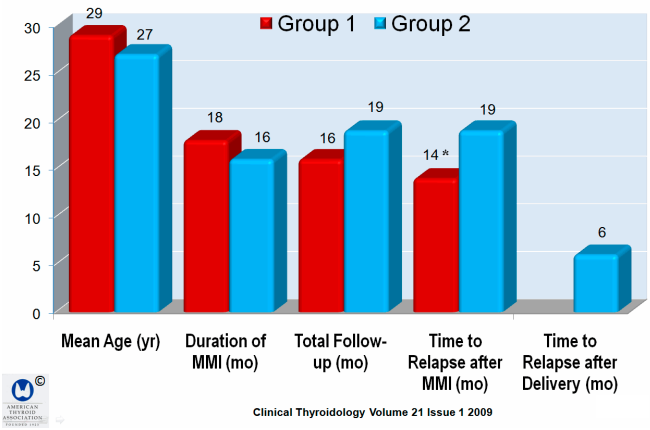

Figure 2. The only significant variable found on multivariate analysis is time to relapse after methimazole withdrawal, which was 14 months in group 1 (range, 6 to 144) and 19 months in group 2 (*P<0.0001). MMI denotes methimazole. Adapted from the data in Table 1 in Rotondi et al.

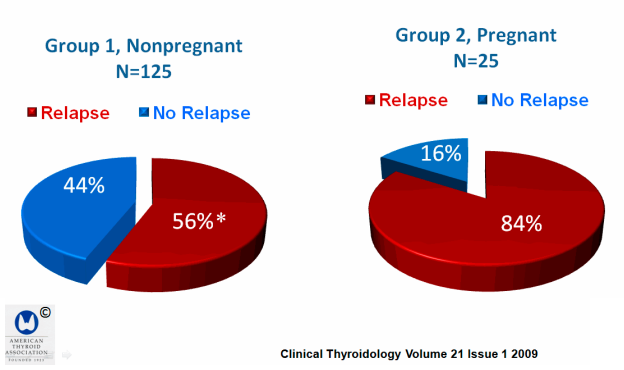

Figure 1. This figure shows relapsing Graves' hyperthyroidism in 21 of 25 patients who had a pregnancy after antithyroid drug (ATD) withdrawal (84.0%) and in 70 of 125 patients who did not become pregnant since ATD withdrawal (56.0%, *P<0.05). Adapted from the data in Figure 1 in Rotondi et al.

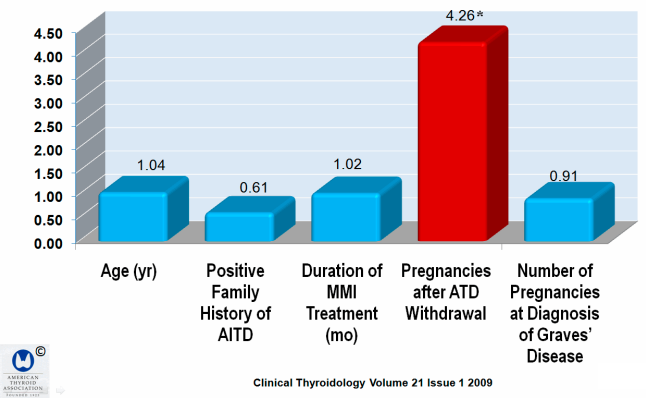

Figure 3. The relative risks for relapsing Graves' hyperthyroidism after antithyroid (ATD) drug withdrawal. MMI denotes methimazole. AITD is autoimmune thyroid disease. Adapted from the data in Table 2 in Rotondi et al.

was significantly lower in group 1 (56%) than in group 2 (84%) (P <0.05; Figure 1). Multiple regression analysis found that the time to relapse after MMI was significantly shorter in group 1 than in group 2 (P<0.0001; Figure 2), indicating that only the number of pregnancies after ATD withdrawal was significantly related to the occurrence of relapsing hyperthyroidism (Figure 3). To discriminate the role of pregnancy and the PP period, the timing of the relapse was further evaluated in the patients in group 2. During gestation, none of the patients in group 2 had a relapse of hyperthyroidism; however, 20 of 21 (95.2%) had a relapse during the PP period, between 4 and 8 months after delivery, whereas only 1 of 21 (4.8%) had a relapse of hyperthyroidism after the PP period (24 months after delivery). Pregnancy was recorded after MMI withdrawal in only 4 of 59 patients (6.8%), who remained in remission throughout the study period. The overall relapse rate of hyperthyroidism after ATD treatment was 60.1%. The relative risk for relapsing Graves' disease after ATD was only significantly higher (4.57, 95% confidence interval, 1.315 to 13.782, P = 0.016) in pregnancies after ATD withdrawal and was not related to a positive family history of autoimmune thyroid disease, duration of MMI treatment, or the number of pregnancies at diagnosis of Graves' disease (Figure 3).

CONCLUSION Pregnant women with Graves' disease in remission after antithyroid drug therapy are at high risk of relapsing hyperthyroidism during the postpartum period

COMMENTARY

Relapse of Graves' hyperthyroidism usually occurs within the first 3 to 6 months after antithyroid drugs are stopped (1) and, over time, is approximately 50%, ranging from 30% to 60% in various studies (1-3). About 75% of women in remission after antithyroid drug therapy who become pregnant will have a relapse of Graves' hyperthyroidism or the development of postpartum thyroiditis 2 to 4 months postpartum (4).

The relapse rate of hyperthyroidism in the study by Rotondi et al. was 60% after antithyroid drug therapy was withdrawn and was significantly higher (84%) in patients who became pregnant after discontinuing the antithyroid drug therapy , compared with a 56% recurrence rate in women who did not became pregnant after discontinuing the drug. None of the patients had a relapse during the first trimester of gestation, whereas more than 95% of pregnant women in whom hyperthyroidism developed after antithyroid drug withdrawal did so during the PP period.

By multiple regression analysis, the relative risk of a relapse (4.26) of hyperthyroidism occurred almost exclusively in pregnant women after antithyroid drug withdrawal, and the results show that relapse of Graves' hyperthyroidism occurs almost exclusively during the postpartum period. None of the patients experienced a relapse of hyperthyroidism during gestation, and in 20 of 21 patients (95.2%), the relapse of Graves' hyperthyroidism occurred between 4 and 8 months after delivery.

Other studies have found that thyroid volume, serum levels of free thyroid hormones and antithyrotropin receptor antibody titers influence the recurrence rate of Graves' hyperthyroidism, but this group of variables was not explored in the Rotondi study. Rotondi et al. provide two caveats: first, thyroid function should be carefully monitored in women with Graves' disease who become pregnant, which is in accord with recent Endocrine Society guidelines (5), and second, definitive treatment with thyroidectomy or radioiodine should be strongly considered in women with Graves' disease who plan to become pregnant. Both seem like excellent options in this setting.

Ernest L. Mazzaferri, MD, MACP

References

1. Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.

2. Torring O, Tallstedt L, Wallin G, et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine—a prospective, randomized study. Thyroid Study Group. J Clin Endocrinol Metab 1996;81:2986-93.

3. Brent GA. Graves' disease. N Engl J Med 2008;358:2594-605.

4. Amino N, Tanizawa O, Mori H, et al. Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. J Clin Endocrinol Metab 1982;55:108-12.

5. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007;92(8 Suppl): S1-S47.