



Dual Cause of Recurrent Pregnancy Loss: Hashimoto's Thyroiditis and Inherited Protein S Deficiency

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Abstract

Recurrent pregnancy loss (RPL) is a rare occurrence in routine medical practice complicating 1-3% of all pregnancies. They represent a real diagnostic challenge due to the multitude of possible etiologies, and remain unexplained in more than 50% of cases. We report the original observation of a 32-year-old Tunisian woman investigated for six recurrent early miscarriages. The investigations concluded with a dual etiology: Hashimoto's thyroiditis (free thyroxine at 6 pmol/l, thyroid-stimulating hormone at 12.4 μ IU/mL, positive anti-thyroglobulin antibodies at 32.8 IU/ml, and positive anti-thyroperoxidase (anti-TPO) antibodies at 677 IU/ml) with inherited thrombophilia (protein S deficiency of 41%).

This association, however rare and unusual, deserves to be recognized by clinicians to avoid diagnostic delays and ensure proper management of recurrent miscarriages.

Keywords: Recurrent Pregnancy Loss; Hashimoto's Thyroiditis; Protein S Deficiency; Inherited Thrombophilia; Recurrent Miscarriages; Anti-Thyroperoxidase (Anti-TPO) Antibodies

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Introduction

Defined as two or more consecutive spontaneous pregnancy losses before 24 weeks of gestation,, recurrent miscarriages or recurrent pregnancy loss (RPL) are a rare occurrence in routine medical practice complicating 1-3% of all pregnancies [1-3]. They represent a real diagnostic challenge due to the multitude of possible etiologies, and remain unexplained in more than 50% of cases [1-3].

The etiologies of these RPLs are dominated by uterine malformations, chromosomal abnormalities, endocrinopathies and acquired thrombophilias, particularly antiphospholipid antibody syndrome [4, 5].

The combination of several of these risk factors in pregnant women significantly increases the risk of pregnancy loss [6].

Through this original observation, we illustrate the association of two rare etiologies of RPL, Hashimoto's thyroiditis (HT) and protein S deficiency, in a young Tunisian woman.

Case Presentation

A 32-year-old woman, with no significant past medical history, was referred by her gynecologist for further investigation of recurrent early pregnancy loss. She had been married for four years and had experienced six early miscarriages. Gynecological examination and uterine imaging were unremarkable. Gonadotropin levels were within normal limits, serological tests for sexually transmitted infections were negative, and basic laboratory tests were normal (fasting blood glucose, complete blood count, creatinine, lipid profile, liver enzymes, uric acid, serum electrolytes, phosphor-calcic parameters, and urinalysis). The patient was referred to us due to suspected antiphospholipid syndrome.

The physical examination revealed no abnormalities; in particular, there was no fever, no mucocutaneous signs of vasculitis, and no synovial or articular lesions.

Immunological tests were negative, ruling out connective tissue diseases and a possible primary or secondary antiphospholipid syndrome: antinuclear antibodies, anti-native DNA antibodies, anti-

soluble antigens antibodies, anticardiolipin antibodies, anti-beta-2-glycoprotein-1 antibodies, anti-annexin V antibodies, and lupus anticoagulant.

Thrombophilia screening showed an isolated protein S deficiency of 41% (normal range at 60–130%). Other tests were normal (normal levels of protein C, antithrombin III, and homocysteine, and no mutations in factor V Leiden or coagulation factor II).

Thyroid function tests revealed hypothyroidism with a thyroid-stimulating hormone (TSH) level of 12.4 μ IU/mL and a free thyroxine level of 6 pmol/L. Thyroid ultrasound showed an atrophic thyroid gland with a heterogeneous structure, and immunological tests confirmed the diagnosis of Hashimoto's thyroiditis with positive anti-thyroglobulin and anti-thyroperoxidase antibodies (anti-TPO) at 32.8 and 677 IU/ml, respectively.

The diagnosis was then made of primary hypothyroidism due to Hashimoto's thyroiditis associated to inherited thrombophilia type protein S deficiency.

The patient was started on low-molecular-weight heparin (4000 IU/day), salicylate (100 mg/day), and thyroxine in progressively increasing doses until TSH normalization at a dose of 125 μ g/day. The outcome was favorable, with a successful pregnancy one month after TSH normalization. The patient subsequently had a second pregnancy, which was carried to term without complications, and no further miscarriages have been recorded in the last five years.

Discussion

Endocrine disorders can account for 8 to 12% of cases of RPL [7]. The main endocrinopathies are hyperprolactinemia, luteal phase deficiency, thyroid dysfunction, diabetes mellitus, insulin resistance, and polycystic ovary syndrome [3, 7, 8].

Hypothyroidism, even subclinical, can be associated with various pregnancy complications [9]; however, chronic Hashimoto's thyroiditis remains an exceptional cause of RPL. It is seen in approximately 0.5% of pregnant women [8, 10]. Indeed, in the large American cohort study by Imbroane MR et al., which included 128,376 women with RPL, Hashimoto's thyroiditis was noted in only 1.04% of cases [11], and in the retrospective observational cohort study by Cellini M et al., the prevalence of RPL in women with Hashimoto's thyroiditis was 2.1% [6].

However, this association remains significant compared to the matched cohort of women without RPL in the series by Imbroane MR et al: 1.04% vs 0.58% ($p < 0.0001$) with a relative risk of 1.82 [11].

Thyroid autoimmunity, independent of thyroid function, is also significantly associated with the occurrence of RPL, particularly the positivity of anti-TPO autoantibodies [2, 3, 12, 13]. This could be explained by the deleterious effect of these autoantibodies on placental cells, as proven by experimental studies in animals: injection of anti-TPO antibodies to female mice was associated to histological delay in fetal development in 50% of cases with significant pathological structural changes in the placenta leading to pregnancy loss [14].

The beneficial effect of TSH-normalizing hormone replacement therapy on RPL is clearly proven, whereas no benefit is noted in women with positive antithyroid autoantibodies and normal thyroid function [3, 12].

RPLs caused by thrombophilias are mostly due to acquired

thrombophilias, primarily antiphospholipid syndrome [4]. Hereditary thrombophilias remain exceptional as a possible cause of RPLs [4].

The relationship between hereditary thrombophilias, particularly Protein S deficiency, and RPLs is highly controversial and often misunderstood due to the physiological existence during pregnancy of a hypercoagulable/prothrombotic state with decreased anticoagulant activity of Protein S and acquired resistance to Protein C [4, 15].

Therefore, protein S deficiency is considered an exceptional and non-classical cause of RPL [2, 15, 16]; indeed, in the meta-analysis by vanDijck MM et al, the pooled prevalence of this hereditary thrombophilia was 5.36% in women who had had two or more abortions [2]. The positive association between protein S deficiency and the occurrence of RPL is, however, well established [17].

Treatment with low molecular weight heparin, sometimes combined with progesterone, allows for successful pregnancies in women who have experienced recurrent miscarriages [2, 3, 16].

The probability of the association of these two possible etiologies of RPL (thyroid dysfunction and protein S deficiency), as in our observation, would be extremely rare. Indeed, the prevalence of these two conditions was 9.5% and 4.3% respectively in the large series of 5708 women with RPL by Morita K et al [18]. The probability of having these two abnormalities would thus be on the order of 0.40%.

Conclusion

Our observation is original due to the association of two rare causes of recurrent pregnancy loss: Hashimoto's thyroiditis and hereditary protein S deficiency. This association, however rare and unusual, deserves to be recognized by clinicians to avoid diagnostic delays and ensure proper management of recurrent miscarriages. Thyroid hormone levels, thyroid autoimmunity testing, and screening for hereditary thrombophilia should be systematically performed in all women presenting with recurrent pregnancy loss.

Conflicts of Interest: None.

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