Levothyroxine and thyroid peroxidase antibodies in women with recurrent pregnancy loss

We recently read with interest the conclusions of the review and meta-analysis (1) that studies the administration of levothyroxine to women with subclinical hypothyroidism and its relationship with pregnancy outcomes, as well as the association of thyroid autoimmunity to recurrent pregnancy loss (RPL). Both topics generate considerable interest among our patients and, very often, confusion among physicians.

The administration of levothyroxine is recommended to treat hypothyroidism—a thyroid hormone deficiency that may or may not have an autoimmune origin—to normalize thyroid function. According to the Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum, 2017 (2, 3), there is no need to treat healthy pregnant women with normal thyroid function using levothyroxine, independently of their thyroid antibody status.

A recent randomized study (4) suggests levothyroxine does not benefit euthyroid women with thyroid autoimmunity. The study is designed based on an unusual hypothesis: decreasing the miscarriage rate using levothyroxine in euthyroid patients.

It is universally agreed that overt hypothyroidism should be treated, as maternal thyroid function is very important for normal embryonic and fetal development, especially neurodevelopment. The association of thyroid autoimmunity to RPL is still controversial.

The present study (1) concluded that thyroid autoimmunity is associated with RPL. Meta-analysis of studies shown on their Table 3 (1) provides data on the association of thyroid peroxidase (TPO) antibodies (Abs) with an increased risk of miscarriage and preterm birth, even with normal thyroid function. It is well known that patients with positive TPO Abs have an increased risk of miscarriage.

The maternal immune system is one of the main actors of the maternal-fetal interface. Its dysregulation in the form of lack of activation or over-reactivity seems to influence placentation and pregnancy outcomes.

Several studies (5, 6) have pointed out an association between antiphospholipid (APL) syndrome (APS) and thyroid autoimmunity (1) (Supplemental Table 3); some of them suggesting common pathophysiologic processes and genetic background. A literature review (5,6) was conducted on existing data on APL/APS and thyroid autoimmune disorders, paying particular attention to the possible role of this association in obstetric complications.

The prevalence of anticardiolipin Abs or lupus anticoagulant was significantly higher in women with than in women without Thyroid autoimmunity (TAI). Antiphospholipid syndrome is an acquired autoimmune thrombophilic condition. It is a cause of pregnancy complications attributable to placental insufficiency, including RPL, intrauterine growth restriction, oligohydramnios, preeclampsia and placental abruption. Patients with APS do not have a higher infertility rate than the general population. However, they do have poorer reproductive outcomes and a higher risk of gestational complications.

Immune dysfunctions, particularly those induced by APL Abs, are known to trigger miscarriage. Their treatment, very well known and widely established, does not include levothyroxine or intravenous immunoglobulin. That is why studies based on treating euthyroid women with RPL and thyroid autoimmunity with levothyroxine failed to show any positive impact on pregnancy outcomes.

The present meta-analysis (1) supports an association between thyroid autoimmunity and RPL. The evaluation of women with RPL should include APL Abs screening in line with current recurrent miscarriage guidelines, paying special attention to women with thyroid autoimmunity and euploid embryo losses.

More studies involving a careful selection of patients, euploid embryo transfers, and autoimmune (TPO Abs and APL Abs), molecular and transcriptomic analysis of molecules involved in placentation are needed to identify whether the presence of thyroid autoimmunity is a marker of an immune imbalance that could affect maternal-fetal tolerance and increase the risk of RPL. At present the complete immune mechanisms of RPL in euthyroid TPO-positive women have not yet been completely uncovered, although there seems to be an association.

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