Association between previously unknown connective tissue disease and subclinical hypothyroidism diagnosed during first trimester of pregnancy

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Objective: To investigate the presence of autoimmune rheumatic disorders among women with autoimmune thyroid disorders diagnosed during the first trimester of pregnancy and subsequent pregnancy outcomes.
Design: Case-control study.
Setting: Tertiary obstetric and gynecologic center.
Patient(s): Pregnant women in the first trimester of pregnancy.
Intervention(s): Clinical, laboratory, ultrasonographic evaluations.
Main Outcome Measure(s): Thyroid-stimulating hormone (TSH) level; antibodies against thyroperoxidase, thyroid globulin and TSH receptor detection; screening for rheumatic symptoms and antinuclear antibodies (ANA); uterine artery pulsatility index evaluation; pregnancy complication onset.
Result(s): Out of 3,450 women enrolled, 106 (3%) were diagnosed with autoimmune thyroid disorders. ANA were present in 18 (16.9%) of 106 cases and 26 (12.6%) of 206 controls. Of the cases, 28 (26.4%) of 106 reported rheumatic symptoms, 5 of these were diagnosed with Sjögren syndrome or with undefined connective tissue disease. Autoimmune thyroid diseases are statistically significantly associated with a higher risk of preeclampsia, fetal growth restriction, and overall pregnancy complications compared with controls, with a higher uterine artery pulsatility index, suggesting a defective placentation in thyroid disorders. The effect of ANA-positivity on moderate/severe adverse pregnancy outcomes was statistically significant among the patients with thyroid disorders (9 of 18 as compared to 8 of 88, odds ratio 9.65; 95% confidence interval, 2.613–7.81).
Conclusion(s): Connective tissue diseases are frequently associated with autoimmune thyroid disorders diagnosed during the first trimester of pregnancy. Thyroid autoimmunity and ANA positivity independently increased the risk of adverse pregnancy outcomes. (Fertil Steril® 2015;104:1195–201. ©2015 by American Society for Reproductive Medicine.)
Key Words: Antinuclear antibodies, pregnancy, subclinical hypothyroidism

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Thyroid function plays a key role during implantation and the early stages of embryo development (1). Thyroid hormones directly modulate the secretion of specific angiogenetic growth factors and cytokines involving in trophoblastic decidual invasion at the beginning of pregnancy (2). Autoimmune thyroid disorders are organ-specific autoimmune disorders defined by lymphocytic infiltration of the thyroid (3) and autoantibodies against thyroid peroxidase (TPO-ab), thyroglobulin (Tg-ab), and thyroid-stimulating hormone-receptor (TR-ab). Autoimmune thyroid disorders

Received June 3, 2015; revised July 23, 2015; accepted July 29, 2015; published online August 19, 2015.
F.B. has nothing to disclose. E.L. has nothing to disclose. C.A. has nothing to disclose. E.L. has nothing to disclose. V.R. has nothing to disclose. M.S. has nothing to disclose. C.C. has nothing to disclose. A.S. has nothing to disclose.
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Fertility and Sterility® Vol. 104, No. 5, November 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.07.1158

are associated with adverse obstetric outcomes resulting from abnormal placentation, such as miscarriage, stillbirth, fetal growth restriction, preeclampsia, and preterm delivery (4).

In nonpregnant women, thyroid autoimmune disorders are often associated with antinuclear antibodies (ANA) (5), which in turn are a marker of rheumatic disorders (6, 7). Autoimmune thyroid and rheumatic disorders are closely associated, sharing similar clinical manifestations (8, 9) and a common genetic and immune pathway (10, 11). Both thyroid and rheumatic disorders have been shown to increase the rates of adverse pregnancy outcomes, including pregnancy failure, prematurity, preeclampsia, and fetal growth restriction (4, 12).

Although the association between autoimmune thyroid and rheumatic disorders has been studied in nonpregnant women (8–11), there are no data on the frequency of this association during pregnancy and its impact on reproductive outcomes. Our study investigated the presence of autoimmune rheumatic disorders among women with asymptomatic, previously undiagnosed autoimmune thyroid disorders during the first trimester of pregnancy and their impact on subsequent pregnancy outcomes.

MATERIALS AND METHODS

Patients

The participants in the study were a subset of pregnant women who had been enrolled in a clinical study on the incidence of previously unknown rheumatic diseases during pregnancy. Each Monday, from May 2009 to January 2013, all the women attending the ultrasonography clinic of our department were considered eligible for enrollment. The study was approved by the local ethics committee of our department (Current Research Project no. 686 of IRCCS Foundation Policlinico San Matteo of Pavia, years 2011–2016). Women with known autoimmune rheumatic disease or thyroid disorders diagnosed before pregnancy were excluded from the study.

At enrollment, all the women were tested for serum thyroid-stimulating hormone (TSH) and autoantibodies against thyroperoxidase (TPO-ab), thyroid globulin (TG-ab), and TSH receptor (TR-ab) according to standard procedures (Immunolite 2000 Systems Analyzer; Siemens Healthcare) (13, 14). When serum TSH levels were higher than 2.5 mU/mL, we also tested free thyroxine (T_4) and free triiodothyronine T_3 (13, 15) levels to evaluate the presence of an overt hypothyroidism. Women with levels of TSH $>$2.5 mU/mL were referred to the endocrinology unit of our hospital for the clinical evaluation and thyroid ultrasound. We considered TPO-ab and TG-ab levels to be positive at $>$40 IU/mL. We considered the levels of TR-ab positive at $>$1.75 U/L.

All the women enrolled in the study were also screened for the presence of a rheumatic disorders. Briefly, we had obtained informed consent and before the medical evaluation, we asked all the Italian women and/or non-Italian women who were fluent in Italian language to complete a screening questionnaire that had been developed to take into account the most common symptoms of rheumatic disorders according to the commonly used classification criteria for systemic lupus erythematosus, rheumatoid arthritis, primary Sjögren syndrome, systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue diseases, small vessel vasculitis, and undefined connective tissue disease. After the questionnaire screening, the women were tested for the presence of circulating autoantibodies including antinuclear antibody (ANA), anti-double-stranded DNA, anti-extractable nuclear antigen, anticardiolipin antibody, anti-β2-glycoprotein I antibodies (aβ2GPI), and lupus anticoagulant. All these autoantibodies were tested according to standardized methods, as previously described elsewhere (16).

The ANA positive samples (titre $\geq$1:80) were evaluated at increasing dilutions in phosphate-buffered saline up to 1:640. Autoantibody-positive women were referred to the rheumatology unit of our hospital for further clinical assessment including a careful history and a physical examination. The rheumatologists were unaware of the results of the questionnaires or of the autoimmune thyroid status. Rheumatic diseases were classified according to widely used criteria for undefined connective tissue disease according to Mosca et al. (17), rheumatoid arthritis (18, 19), systemic lupus erythematosus (20), antiphospholipid syndrome (21), Sjögren syndrome (22), systemic sclerosis (23), polymyositis/dermatomyositis (24), and mixed connective tissue diseases (25). Patients with suspected connective tissue disease who did not fulfill our criteria were classified as no criteria for a diagnosis group. All the women enrolled in the study were booked for antenatal care and were delivered at our institution.

Uterine artery pulsatility index (UA PI) was evaluated according to standard methods (26) at the first and second trimester of pregnancy. Doppler velocimetry of the UA was evaluated using 3.55-MHz curvilinear transabdominal probe, and the size of the sampling gate was set to 2 mm. A midsagittal section of the uterus was examined, and the cervical canal was identified. The probe was moved laterally until the paracervical vascular plexus was seen. Color Doppler was turned on, and the UA was identified as it turned cranially to make its ascent to the uterine body. Measurements were taken at this point, before the UA branched into the arcuate arteries. Once we had ensured that the angle of insonation was $<60^{\circ}$, the pulsed Doppler gate was placed over the vessel, and the signal was recorded until at least three consecutive flow velocity waveforms of good quality were obtained. The mean PI for left and right UA were obtained by averaging the value of three consecutive measurements. Abnormal UA Doppler was defined by the mean PI above the 95th percentile.

Preeclampsia and gestational diabetes were diagnosed according to standard criteria (27, 28). Fetal growth restriction was diagnosed when abdominal fetal circumference fell below the 10th percentile of our local intrauterine growth curve and the umbilical artery Doppler PI was greater than the 95th percentile of our reference curve (29). A small-for-gestational age (SGA) infant was diagnosed when the sex/adjusted birthweight was below the 10th percentile of the Italian population.

Statistical analyses were performed with one-way analysis of variance and the Bonferroni post hoc test to compare continuous variables between the groups studied. We used