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Connective tissue diseases and autoimmune thyroid disorders in the first trimester of pregnancy

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ABSTRACT

Objective: To investigate the rates and coexistence of autoimmune thyroid and connective tissue diseases (CTD) during the first trimester of pregnancy and their influence on pregnancy outcome.
Study design: A cohort study of 150 women with CTD diagnosed during first trimester of pregnancy and 150 negative controls.
Main outcome measures: Screening of CTD by a self-reported questionnaire, rheumatic and thyroid autoantibody detection, clinical rheumatological evaluation and obstetric outcomes.
Results: Out of 3852 women screened, 61 (1.6%) were diagnosed with undefined connective tissue disease (UCTD), 28 (0.7%) with major CTD (six rheumatoid arthritis, five systemic lupus erythematosus, eight Sjogren syndrome, five anti-phospholipid syndrome, two systemic sclerosis, one mixed CTD and one monoarticular arthritis) and 61 (1.6%) had insufficient criteria for a diagnosis of a rheumatic disease. The overall prevalence of either thyroid peroxidase (TPO-a) or thyroglobulin (TG-a) autoantibodies detection was 8% (12/150) among controls, 62.3% (38/61) among UCTD and 60.7% (17/28) in women with a major CTD ($p < .001$ compared to controls for both comparisons). After adjustment for confounders, overall CTDs (major or undefined) (OR = 3.54, 95% CI; 1.61–7.78) and TPO-a plus TG-a positivity (OR = 2.78, 95% CI;1.29–5.98) were independently associated with increased risks of moderate–severe complications of pregnancy (miscarriage, fetal growth restriction, preeclampsia, delivery before 34 weeks).
Conclusions: Rheumatic and thyroid autoantibodies during pregnancy are closely associated. Thyroid antibodies could add to the risk of adverse pregnancy outcome associated with connective tissue diseases.

1. Introduction

Thyroid disorders, defined as hormonal abnormalities or the presence of thyroid antibodies against thyroglobulin (TG-a), thyroid peroxidase (TPO-a), or thyrotropin receptor autoantigens (TR-a), are common pregnancy-related diseases, present in almost 2.7% of all pregnant women (Baba and Azar, 2012). They are associated to adverse obstetric outcomes, such as spontaneous abortion, fetal death, fetal growth restriction, preeclampsia, gestational diabetes and preterm delivery (Saki et al., 2014). Autoimmune thyroid disorders are frequently associated with other organ and non-organ-specific autoimmune diseases, including autoimmune connective tissue disease (Tagoe, 2015).

Autoimmune connective tissue diseases are more common among women of childbearing age and have been associated with increasing pregnancy complications such as miscarriage, premature delivery and fetal growth restriction (Spinillo et al., 2012; Beneventi et al., 2012).

In general population many studies have suggested an association between thyroid and connective tissue diseases (Tektonidou et al., 2004; Acay et al., 2014; Boelaert et al., 2010). Rheumatologic manifestations such as arthritis, arthralgia and muscle pain are commonly described in autoimmune hypothyroidism (Tagoe

Abbreviations: CTD, connective tissue diseases; UCTD, undefined connective tissue disease; TPO-a, thyroid peroxidase autoantibodies; TG-a, thyroglobulin autoantibodies; TR-a, thyrotropin receptor autoantigens; TSH, thyroid stimulating hormone; PI, pulsatility index.

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et al., 2013). On the other hand, thyroiditis is often associated with other autoimmune diseases such as rheumatoid arthritis (Lazurova et al., 2014), systemic lupus erythematosus (Rudrajit et al., 2012), mixed connective tissue disease, systemic sclerosis (Antonelli et al., 2013) and Sjogren's syndrome (Amador-Patarroyo et al., 2012; D'Arbonneau et al., 2003). The pathogenic mechanisms of this coexistence are not completely defined, but genetics, immune defects, hormonal and environmental factors may play key roles in polyautoimmunity (Lazurova and Benhatchi, 2012).

Although either thyroid or rheumatic autoimmune disorders have been associated with pregnancy complications, there are no data on the effect of the association between the two disorders on pregnancy outcome.

The purpose of our study was to investigate the rates and coexistence of autoimmune thyroid and autoimmune connective tissue disorders in women during the first trimester of pregnancy and to evaluate their effect on pregnancy outcome.

2. Materials and methods

2.1. Study population and design

Women for the study were recruited among unselected pregnant women who booked for antenatal care at our Department during the first trimester of pregnancy. As this was a cohort pilot study involving only a few members of staff, we restricted the enrolment to all women attending the clinic for antenatal care each Monday during a 5-year period (May 2008–June 2013). The study was approved by the local ethics committee of our Department (Current Research Project N.686 of IRCCS Foundation Policlinico San Matteo of Pavia years 2011–2016). Enrolment criteria included: (a) singleton pregnancy; (b) antenatal care and delivery at our Department; (c) fluency in Italian language; (d) no previous diagnosis or treatment of connective tissue diseases. The characteristics of the study and the validation of the methods used have been already reported elsewhere (Spinillo et al., 2008, 2012).

2.2. Clinical evaluation, antibodies detection, obstetric variables

After an informed consent and before the medical evaluation, each woman was asked to complete a screening questionnaire including main connective tissue disorders symptoms (Fig. 1). Women who answered positively to one or more of the questions constituted the cases and were tested for the presence of circulating autoantibodies including antinuclear antibody, anti-double-stranded DNA, anti-extractable nuclear antigen, anticardiolipin antibody, anti-β2-glycoprotein I antibodies and lupus anticoagulant, according to standardised methods, as previously described (Spinillo et al., 2008). To ensure random sampling, the first woman with negative responses to all the items in the questionnaire after each index case and willing to participate into the study, was tested for autoantibodies and served as control. Cases and controls were referred to the rheumatology unit of our hospital for further clinical assessment including a careful history and a physical examination. During first trimester both cases and controls were tested for serum thyroid stimulating hormone (TSH), TPO-a, TG-a and TR-a according to standard procedures (Immunolite 2000 Systems Analyzers) (Hay et al., 1991; Becker et al., 1985). If serum TSH levels were higher than 2.5 mU\ml, we tested also serum fT4 and fT3 (Hay et al., 1991; Albertini and Ekins, 1982) levels to evaluate the presence of an overt hypothyroidism or hyperthyroidism. Rheumatic diseases were classified according to widely used criteria for UCTD (Mosca et al., 1999), rheumatoid arthritis (Visser et al., 2002), systemic lupus erythematosus (Hochberg, 1997), antiphospholipid syndrome (Miyakis et al., 2006), Sjogren's syndrome (Vitali et al., 2002), systemic sclerosis (Masi, 1988) and mixed connective tissue disease (Alarcón-Segovia and Cardiel, 1989). Patients with suspected CTD not fullfilling the above-mentioned criteria were classified as no criteria for a diagnosis group.

All cases and controls were followed since the first trimester of pregnancy to the delivery, to evaluate the onset of complications. Mean uterine artery pulsatility index (PI) at first and second trimester was evaluated according to standard methods (Khalil and Nicolaides, 2013). Abnormal uterine artery Doppler was defined by the mean PI above the 95th percentile.

Preeclampsia, gestational diabetes and fetal growth restriction were diagnosed according to standard criteria (Davey and MacGillivray, 1988; American Diabetes Association, 2012; American College of Obstetricians and Gynecologists, 2008). Small for gestational age infant was diagnosed when sex/adjusted birth weight was below the 10th percentile of the Italian population.

2.3. Statistical analysis

Statistical analyses were carried out with one-way analysis of variance and Bonferroni post-hoc test to compare continuous variables between the groups studied. Two-way analysis of variance was used to evaluate the independent effect of thyroid autoantibodies and rheumatic diseases on continuous variables. We used log-transformed data when assumptions on normality were not met. Categorical variables were tested by Pearson's χ^2 or Fisher's exact test, when appropriate. Partitioning of χ^2 statistics with Bonferroni correction for multiple comparisons was used to evaluate the statistical significance of pairwise comparisons in $2 \times K$ tables. Associations between thyroid antibodies status and rheumatic diseases, and the association between these two variables and pregnancy outcomes were analysed using penalized logistic regression by computing odds ratios and 95% confidence intervals adjusting for potential confounders (Stata 12.0 for Windows (StataCorp LP, College Station, TX, USA). Penalized maximum likelihood estimation has been proposed as a suitable method of regression analysis for uncommon events (Wang, 2014). Pregnancy-related complications were categorized as moderate/severe (miscarriages or intrauterine fetal death, fetal growth restriction, preeclampsia, delivery before 34 weeks of gestation) or overall adverse outcomes (moderate/severe adverse outcome, delivery before 37 weeks of pregnancy, small for gestational age infant, gestational diabetes) and were inserted as outcome variables in logistic regression models. Explanatory variables included maternal age, nulliparity (yes, no), smoking at first trimester of pregnancy (yes, no), diagnostic category of rheumatic disease (controls, UCTD, major connective tissue disease, insufficient criteria for diagnosis) and detection of TPO-a and/or TG-a.

3. Results

3.1. Rheumatologic evaluation

Out of 4031 women who booked for antenatal care at our institution in the recruitement dates, 3852 (95.5%) eligible women agreed to answer to the questionnaire and participate to the study. The median gestational age at enrolment was 12.3 weeks (range 11.5–13.4). Out of 471 (12.2%) women who answered positively to one or more questions, 150 (3.9%) women tested positive for autoantibodies and constituted the cases. Sixty-one women (1.6%) were diagnosed with UCTD, 28 (0.7%) with major rheumatic diseases and 61 (1.6%) had insufficient criteria for a definite diagnosis of a rheumatic disease. Major rheumatic diseases included six women with rheumatoid arthritis, five with systemic erythematosus lupus, five with antiphospholipid syndrome, eight with