Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: The role of autoimmunity and thyroid function

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ABSTRACT. Thyroid dysfunction and the presence of thyroid antibodies increase the risk of infertility and miscarriage. The aim of the present study was to assess if patients with autoimmune thyroid disease undergoing assisted reproduction technologies (ART) are afflicted by poor pregnancy and/or delivery rate and if the outcome is conditioned by pre-ART thyroid status. The study was retrospective (from January 2000 to January 2005) and was carried out at the Division of Physiopathology of Human Reproduction. Women who underwent ART were tested for TSH, free T₄ (FT₄), thyroid peroxidase antibodies (TPOAb) before and during pregnancy. A total of 416 euthyroid women were selected; 42 (10.1%) were TPOAb (+). Women >35 yr were excluded. The endpoints were pregnancy and delivery rates. Results: no differences in pregnancy and delivery rates were observed between women with and without antibodies. In TPOAb (+), women who failed to become pregnant or miscarried displayed higher TSH values before ART (2.8 mIU/l) compared to the ones who delivered (1.6 mIU/l; p=0.032) and compared to TPOAb (-) (1.1 mIU/l; p=0.018). Conclusions: in euthyroid women undergoing ART the pregnancy and delivery rates are not affected by the presence of TPOAb. In TPOAb (+) high-normal TSH values are associated with increased risk of unsuccessful pregnancy or subsequent miscarriage. Further studies are required to ascertain possible benefits of levo-T₄ (L-T₄) in such patients. (J. Endocrinol. Invest. 30: 3-8, 2007)

INTRODUCTION

Infertile women who are positive for thyroid autoimmunity (TAI) display two intriguing features: antibodies as markers of an immune disorder and, even if euthyroid, a predisposition to an impaired thyroid function during gestation. Concerning the association of TAI with infertility, conflicting data have been published. Even if the reports about this matter are very heterogeneous, a metaanalysis performed by Poppe and Glinoer (1) clearly showed that women with TAI have a significantly increased risk of infertility. Furthermore, during pregnancy these subjects are likely to suffer from an increased miscarriage rate and recurrent abortions (2, 3). The relationship between hypothyroidism and infertility is clearer, as a normal thyroid function is necessary for a physiologic ovarian function, while during gestation, even mild hypothyroidism is associated with abortion and pre-term delivery (4, 5). In fact, when hypothyroidism is not promptly diagnosed and/or when levo-T₄ (L-T₄) treatment is not adequate during pregnancy an increased rate of obstetric complications has been observed (6, 7). Consequently, autoimmunity and thyroid impaired function seem to represent two sides of the same coin in which these two explanations for infertility and/or poor pregnancy outcome are not mutually exclusive. The aim of the present study was to investigate if: 1) TPOAb (+) women undergoing assisted reproduction technologies (ART) suffer from poor pregnancy rate; 2) thyroid status may influence ART success and delivery rate.

MATERIALS AND METHODS

We retrospectively analyzed data about infertile women who underwent the first ART procedure between January 2000 and Janu-
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The ages ranged from 20-35 yr. We excluded women >35 yr to avoid older age being a confounding factor on outcomes. Causes of infertility were as follows: male origin (50%), ovarian dysfunction (9%), tubal factors (17%), endometriosis (11%) and idiopathic (13%) ones. All patients were screened for the presence of thyroid peroxidase antibodies (TPOAbs), serum TSH, and free T4 (FT4) before undergoing ART. Women with overt thyroid dysfunction were excluded. Of the 423 women selected, 49 (11.6%) were positive for TPOAb. Thyroid function tests were successively checked at 12 and 30 weeks gestation.

All patients received controlled ovarian superovulation. Recombinant FSH (rec-FSH) (Puregon, NV Organon, The Netherlands) and GnRH antagonist (Orgalutran; NV Organon) were used for ovarian stimulation. Starting on day 2 of the menstrual cycle at 200 IU per day, the rec-FSH dose remained the same in all patients during stimulation. Ovulation triggering was performed using 10,000 IU of human chorionic gonadotropin (hCG) (Pregnyl, NV Organon) as soon as at least three follicles 17 mm were present on US scan. Using conventional in vitro fertilization (IVF), each oocyte was inseminated within 3-4 h after retrieval by adding 5,000-20,000 motile spermatozoa per oocyte. If the semen sample on the day of oocytes recovery contained few motile spermatozoa, intra-cytoplasmic sperm injection was performed. For each cycle, five to seven oocytes were retrieved by the vaginal route and after fertilization one to three embryos were transferred depending on their morphological quality. Pregnancy was diagnosed on two occasions at least 10 days after transfer by raising hCG levels by at least 20 IU/ml in the serum. Clinical pregnancies were diagnosed by ultrasonography performed 5 weeks after embryo transfer. The endpoints were pregnancy and delivery rates.

All the patients gave written informed consent for utilization of their data.

Serum TSH and FT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Mannheim; Germany). The reference values were 0.27-4.2 mIU/l for TSH and 9.3-18.0 ng/l (12-33.5 pmol/l) for FT4. TPOAb was determined using a RIA kit (B.R.A.H.M.S. Diagnostica, Berlin, Germany). The reference range was 0-100 kU/l. TPOAb titers were considered positive when titers exceeded 100 kU/l.

Statistical analysis was performed using an SPSS (SPSS, Inc., Chicago, IL) program. Mean TSH values were calculated after log transformation of the individual data and statistical analysis was carried out using analysis of variance (ANOVA). Outcome evaluation was performed using χ² test. Correlations between variables were assessed using Spearman’s test. All statistical tests were considered statistically significant whenever p<0.05.

RESULTS

Distribution of causes of female infertility was not different between groups. There were no differences between groups concerning the number of oocytes retrieved (TPOAb (−) 5.8±1.0; TPOAb (+) 5.8±1.1; p=ns) and embryos transferred (TPOAb (−) 2.2±0.6; TPOAb (+) 2.3±0.6; p=ns). The age was similar between TPOAb (−) and TPOAb (+) (30.1±1.9 and 32.2±1.4 yr, respectively; p=ns).

Thyroid function

In TPOAb (+) women, TSH values before ART, at 12 and 30 weeks were higher than TPOAb (−) (p=0.021; 0.0048; 0.0013, respectively) (Fig. 1, upper panel). Notably, at 30 weeks 7 out of 24 patients with antibodies had TSH comprised between 2.5 and 4.2 mIU/l, while 3 out of 24 showed values above the upper limit. The same group also had FT4 values lower than TPOAb (−) at 30 weeks gestation (p=0.028); 5 out of 24 and 7 out of 24 patients belonging to the TPOAb (+) group showed at 12 and 30 weeks, respectively, FT4 values <9.3 ng/l (Fig. 1, lower panel).

In thyroid antibodies positive women who delivered, TPOAb titers decreased by 66% (from 1286 to 433 kU/l) (Fig. 2).

Pregnancy and delivery rates

Our study showed that pregnancy and delivery rates were not significantly affected by autoimmunity or thyroid function (Fig. 3). The pregnancy and delivery

![Graph showing TSH values as a function of gestational time](image1)

![Graph showing FT4 values as a function of gestational time](image2)

Fig. 1 - Thyroid function values before and during gestation in women with and without thyroid antibodies. Upper panel: TSH values [TPOAb (+) displayed higher values than TPOAb (−) at each time point before and during pregnancy]. Lower panel: FT4 values [TPOAb (+) displayed lower values than TPOAb (−) at 30 weeks]. TPOAb: thyroid peroxidase antibodies.