Effect of autoimmune thyroid disease in older euthyroid infertile woman during the first 35 days of an IVF cycle

In this case-control study of euthyroid first-cycle IVF patients ≥38 years old with singleton baby, miscarriage, biochemical pregnancy, and no pregnancy outcomes from 2005–2008, we assayed frozen serum for autoimmune thyroid disease (AITD) and thyroid function at cycle start, trigger, and 4 and 5 weeks' gestation. AITD prevalence in older infertile women was similar across clinical outcomes, and although AITD was associated with a higher baseline TSH, TSH remained within acceptable ranges, suggesting that T_4 supplementation may not affect maternal outcomes in older euthyroid AITD patients through 5 weeks gestation. (Fertil Steril® 2011;95:1178–81. ©2011 by American Society for Reproductive Medicine.)

Key Words: Thyroid autoimmunity, hypothyroidism, subclinical hypothyroidism, infertility, IVF, thyroid peroxidase antibody, thyroglobulin antibody, miscarriage

The prevalence of autoimmune thyroid disease (AITD) has been reported to increase with age (1) and to be higher in infertile populations (2). Although no apparent effect of AITD has been observed on pregnancy rates (3, 4), many studies (5–7) have concluded that even in the absence of overt thyroid dysfunction, AITD is associated with a three- to fivefold increase in the overall miscarriage rate among women with spontaneous pregnancies. An increased rate of miscarriage has also been observed in most (3, 8–10), but not all (11, 12), studies of women with AITD undergoing assisted reproductive technologies (ART). It has been proposed that the rapid and robust rise in E_2 concentrations with ART may pose a great stress on the hypothalamic-pituitary-thyroid axis and challenge the ability of the thyroid to maintain a pregnancy (13–15), particularly in women with AITD. Women with AITD may have a slightly higher (but still normal) TSH than women without AITD before pregnancy (16), which could lead to subclinical or overt hypothyroidism (14) and poor pregnancy outcomes after ART.

Our aims were to estimate the prevalence of AITD in an older infertile female IVF population to determine if an association exists between the presence of AITD and IVF outcomes and to compare the effect of gonadotropin stimulation and early pregnancy on thyroid reserve in these older women with and without AITD.

We identified the first fresh IVF cycle of all patients ≥38 years old from January 2005 through December 2008 who consented to research performed on discarded tissue specimens (IRB#6902). Patients were categorized into four outcome groups: 1) Baby: singleton pregnancy with singleton live birth; 2) Miscarriage: loss of pregnancy (positive sac) at <13 weeks' gestation; 3) Biochemical Pregnancy (positive hCG but no sac seen on sonogram); 4) No Pregnancy. We excluded spontaneous reductions and multiple gestations in an effort to limit confounding effects of hCG and E_2 on TSH levels. We excluded those with a history of thyroid disease, hyperprolactinemia, and cycles involving preimplantation genetic diagnosis (PGD). Polycystic ovarian syndrome (PCOS) and diminished ovarian reserve, the latter broadly defined as a history of poor response to gonadotropin stimulation and/or day 2 FSH >13.5 mIU/mL, were categorized as ovarian etiologies. IVF cycle preparation, stimulation, embryo culture, embryo transfer, and luteal support protocols were performed as previously

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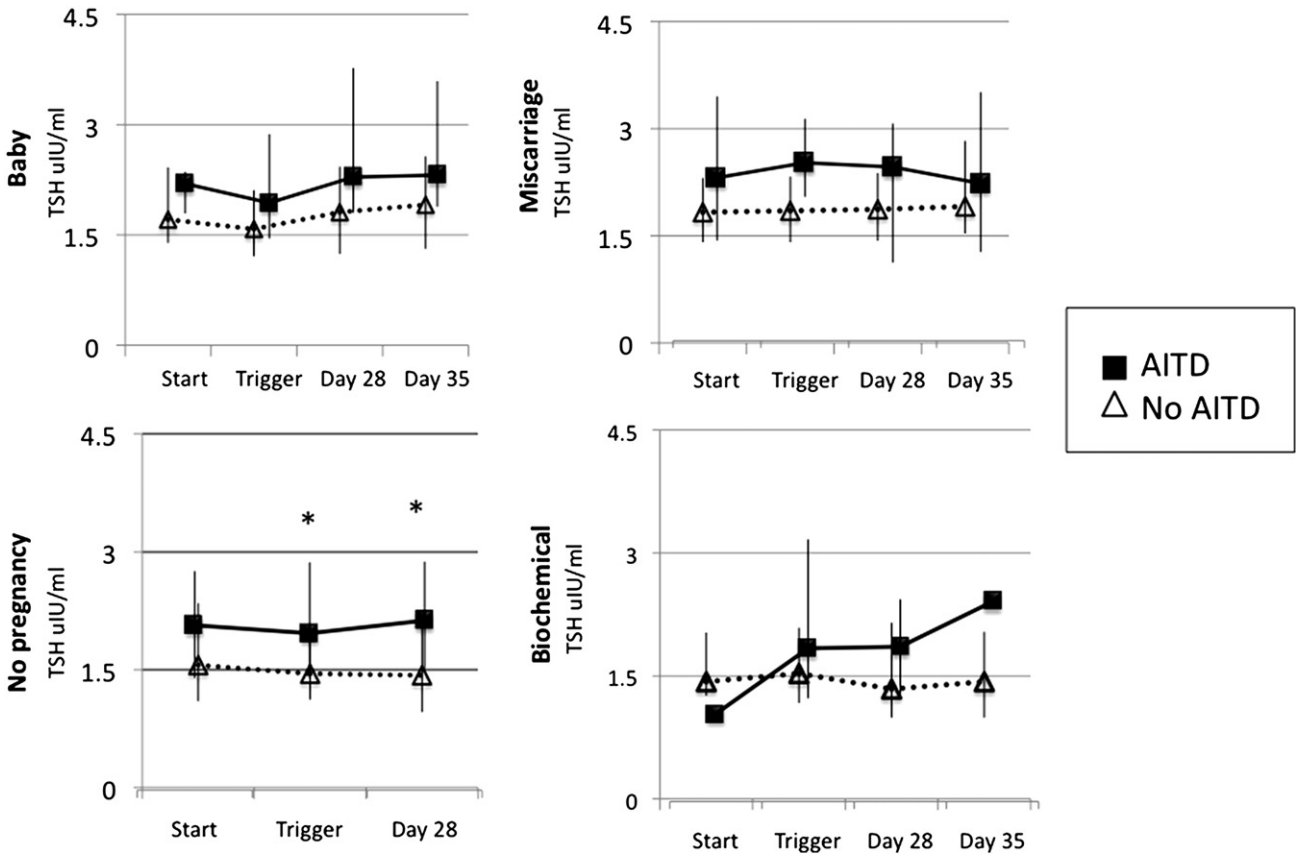
FIGURE 1

Effect of autoimmune thyroid disease (AITD) on changes in TSH from the start of the IVF cycle through day 35. Median values with interquartile ranges are plotted.



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described (17, 18). The number of embryos transfered was in accordance with current American Society for Reproductive Medicine guidelines (19). Delivery follow-up was confirmed directly with patients.

Each patient's previously frozen serum samples were tested for thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb). Thyroid function tests were performed at four times during the IVF cycle: 1) start of IVF cycle (day 2); 2) day of hCG trigger, 3) day 28 (4 weeks' gestation, 14 days after retrieval); and 4) day 35 (5 weeks' gestation, only in patients with a positive day-28 pregnancy test). Thyroid function tests included TSH, free thyroxine (FT_4), thyroxine-binding globulin (TBG), and total thyroxine (TT_4). All assays were conducted at our center's on-site endocrinology lab using an Immulite 2500 machine (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Normal TPOAb levels were defined as <35 IU/mL and normal TGAb levels as <40 IU/mL. AITD was defined as having either positive TPOAb or positive TGAb.

Independent-sample *t* tests, Fisher exact, and chi-square tests were performed as appropriate. Thyroid function data were positively skewed, necessitating the use of statistical procedures that were robust against nonnormality. Generalized linear models were used for repeated-measures analyses with fixed effects of AITD status and time and repeated observations for each patient. Wilcoxon rank sum tests with a Bonferroni correction were used to compare groups regarding thyroid response each time point and changes in TSH levels within each patient from time point to time point. A P value of $< .05$ was considered to be significant, using two-sided tests. Analyses were conducted using SAS vesion 9.2.

Our deidentified retrospective study was approved for expedited review by the New York University School of Medicine Institutional Review Board (IRB # 10–00052), and no investigators declared a conflict of interest.

Among 390 euthyroid patients ≥38 years old (mean ± SD: 41 ± 2 years; range: 38–47 years), 12% (47/390) were positive for TPOAb, 4.6% (n = 18) were positive for TGAb, and 3.0% (n = 12) were positive for both TPOAb and TGAb. A total of 13.6% (n = 53) met our definition for AITD by testing positive for either TPOAb or TGAb.

Comparing those with and without AITD, there was no difference in mean age (both 41 years), gravidity, (64% vs. 69%) parity (21% vs. 32%), BMI (23 vs. 24 kg/m^2), or day 2 FSH levels (8 vs. 7 mIU/mL). There was no difference in the proportions of patients with and without AITD with infertility due to endometriosis