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ASSISTED REPRODUCTION TECHNOLOGIES

Thyroid stimulating hormone levels rise after assisted reproductive technology

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Abstract
Purpose The goal of this study was to determine whether high E2 levels after controlled ovarian hyperstimulation affect TSH.
Methods Patients completing ART cycles between April-October 2010 were eligible for this cohort study. 180 patients were recruited however those with known thyroid disease were excluded. The final analysis included 154 subjects. Blood was collected at each visit during the ART cycle as well as at the pregnancy test. Samples were frozen at −20 °C and analyzed together for E2 and TSH using the same assay kit once all patients had completed their cycles. All participants were treated at the McGill University Health Center. A paired t-test was used to study the difference in TSH levels recorded at maximal and minimal Estradiol levels during ovarian stimulation. Multiple regression analysis was then used to determine if factors such as anti-thyroid antibodies and ovarian reserve measures affect this change in TSH. We used multiple imputation methods to account for missing data.
Results As E2 levels rose from low to supra-physiologic levels during treatment, TSH levels also rose significantly. This increase was clinically significant by the time of pregnancy test. The factors that potentially affected the change in TSH were: male factor/tubal factor infertility, type of protocol used as well as the presence of thyroid antibodies.
Conclusions Although TSH increases during ART, this change only becomes clinically significant on the day of pregnancy test. Future studies should examine TSH changes specifically in certain "at-risk" sub-groups such as those with antibodies and known thyroid disease.

Capsule As estradiol levels rise during ART, TSH also rises. This rise may be affected by: cause of infertility, type of protocol used as well as the presence of anti-thyroid antibodies.

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Introduction

Thyroid Stimulating Hormone (TSH) levels are maintained constant through negative feedback mechanisms involving the hypothalamic-pituitary-thyroid gland axis. It is generally accepted that TSH levels are a "sensitive marker for thyroid gland dysfunction" [19]. Hypothyroidism, both overt and subclinical, affects 3–5 % of reproductive-aged women [6, 16]. The effects of overt hypothyroidism on fertility include impaired ovulation [13], lower clinical pregnancy rates after assisted reproductive technology (ART) [17], higher miscarriage rates [5] and poor obstetrical outcomes [1, 4]. In early pregnancy, high human chorionic gonadotropin (HCG) levels stimulate thyroid function through their receptor homology. However, healthy women do not become overtly hyperthyroid due to compensatory mechanisms involving the hypothalamic-pituitary-thyroid axis as well as increased thyroid binding globulin (TBG) levels [30]. In fact, this increased TBG [11] not only counteracts the effects of HCG but actually stimulates a rise in TSH levels that reach a maximum in the second trimester [12]. Given the importance of thyroid function during pregnancy, TSH levels should be maintained below 2.5 mIU/L in order to control for these changes [8].

During controlled ovarian hyper stimulation (COH) for assisted reproductive technology (ART) i.e. in-vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) cycles, Estradiol (E2) levels rise well above physiologic range. This change occurs prior to the occurrence of a pregnancy and maximal E2 levels often approach 10,000 –12,000 pmol/L, levels comparable to those seen in late pregnancy and significantly higher than those at ovulation [10]. In fact, serum E2 levels during ART reach those seen during the second trimester of pregnancy [25, 26]. There exists literature supporting the concept of a "stress" on the gland and the resultant need to increase thyroxine doses in hypothyroid pregnancies [2, 18]. However, there exist only a few studies assessing these changes during IVF in euthyroid patients. A systematic review of thyroid function during ART was inconclusive and highlighted the need for further studies [20]. Another recent study involving 57 patients showed TSH levels rise after IVF reaching a peak 1 week after HCG trigger[14].

This large, prospective study was designed to evaluate the effect of supra-physiologic E2 on TSH levels during ART cycles in patients with normal thyroid function. We chose to follow TSH as our measure of interest because it is the most commonly performed screening test for thyroid gland dysfunction. We also studied whether various patient characteristics such as ovarian reserve parameters, presence of thyroid-antibodies and etiology of infertility made subjects more susceptible to changes in TSH.

Materials and methods

Patient recruitment

All patients undergoing IVF or ICSI (using their own oocytes) at the McGill University Health Center between April and October 2010 were eligible to participate in this prospective study. Exclusion criteria included those patients with known thyroid disease and those who had previously participated in the study. Informed written consent and ethics review board approval was obtained. Patients who underwent multiple treatment cycles during the study were only included once.

IVF treatment protocols

One of three ART protocols was prescribed prior to enrollment in the study: the long protocol, microdose flare or antagonist protocol. The protocol was decided upon by the patients' attending physician prior to enrollment in the study according to age, ovarian reserve and previous history. Ultrasounds were performed to confirm down-regulation in the long and microdose flare protocols and on cycle day 2 in antagonist cycles. Once gonadotropins were started, ultrasounds and blood tests for serum E2 determination were performed 6 or 9 days later to evaluate ovarian response. Further ultrasounds were prescribed as deemed necessary by the attending physicians. HCG trigger was administered once at least 2 follicles reached 18 mm and oocyte retrieval was performed approximately 36 h later. Micronized progesterone was used as luteal support. Serum HCG was measured 16 days after oocyte collection and, if positive, a viability ultrasound was performed 14 days later.

Blood sample collection and TSH assay

Clinic nurses drew blood samples to monitor serum E2 levels in the morning of the initial and all subsequent ultrasounds during their treatment. Most patients had between three and five ultrasounds, including the initial scan on day two or three of menstruation. In addition, seven had six scans and another patient required a seventh. Blood was drawn at each ultrasound (which included the HCG trigger day) as well as when they returned for their pregnancy test. After serum E2 or HCG levels were recorded, the remainder of the sample was frozen at −20 °C. Once all subjects completed their treatment cycles, samples were thawed and analyzed for TSH. The assay used for TSH during and after ART treatment was a third-generation TSH assay (Siemens Inc., Montreal, Canada). The range of normal for this assay is 0.4–4.40 mIU/L. Its analytical sensitivity is 0.004 mIU/L and the coefficient of variation for mean 1.3 mIU/L was 4.6 %. There was no detectable cross-reactivity with FSH, LH or HCG. The same assay kit from the same lot was used to analyze all samples in order to avoid inter-assay variability. Assays were run using a single apparatus, the

Immulite2000. When measuring anti-thyroid antibodies, we used the Beckman Coulter Access systems TPO Antibody Assay. Patients with antibodies of>9.0 IU/mL were considered "antibody-positive" at our centre.

Statistical methods

Sample size calculation assumed an average TSH value of 2.5 mIU/L in our population and an expected change over the course of stimulation to be 0.5 mIU/L. Assuming a standard deviation of 1.25 mIU/L and a desired detectable change in TSH within an accuracy of 0.2 mIU/L (which gives a 95 % confidence interval) significant. This required a sample size of 150 patients. We collected samples from 180 patients in order to compensate for those who dropped out or whose treatment cycles were canceled for whatever reason. We also specifically excluded patients with known thyroid disease. The final number of subjects included in our analysis totaled 154.

Multiple linear regression modeling was used to investigate risk factors for changes in TSH levels. The outcome of interest, change in TSH levels, was defined as the difference between TSH levels at the maximum level of E2 minus the TSH at the minimal E2 level achieved during ovarian stimulation. The independent variables (or risk factors) that were included in the model were: the presence of anti-thyroid antibodies, age, body mass index (BMI), cause of infertility (unexplained, anovulatory or male factor/endometriosis/tubal factor), antral follicle count (AFC), baseline follicle stimulating hormone (FSH), parity, aborta and pregnancy outcome (negative, positive or ectopic/pregnancy, no HCG test done) as well as protocol used (long versus short). These covariates were included because each was hypothesized to have a potential effect on the change in TSH during treatment. Specifically, those with thyroid antibodies were expected to have a greater change in their TSH in response to COH. Also, the other covariates such as antral follicle count and cause of infertility were theorized to have an impact on changes in TSH levels due to endocrine differences among these various sub-groups. E2 min and max were not considered as covariates because they were included in the definition of the dependent variable.

Of the 154 patients included in the study, 48 patients had missing data on one or more of the continuous variables (2 were missing "TSH at minimum E2", 2 were missing "TSH at max E2", 21 were missing "AFC baseline", 26 were missing BMI, 5 were missing <. "FSH at baseline", and 3 were missing "antibodies at baseline". Multiple Imputation (MI) [29] was used to substitute for the missing values. We used IVEware software for imputation and the SAS procedure MIANALYZE (SAS Institute Inc, Cary, NC) for analyzing the data after imputation. All variables that were to be included in the regression analysis were used in the imputation process. The MI assumption that data is missing at random was reasonable for all independent variables in this study with the exception, perhaps, of BMI because it was a self-reported characteristic. Sensitivity analysis was carried out to evaluate possible bias in the analysis from including BMI in the MI procedure. Furthermore, as a test of robustness, we analyzed the data using Inverse Probability Weighting (IPW) [15]. This is an alternative to MI where only those subjects with complete data are considered and weights are used to make the complete cases more representative of the whole sample. All analyses were done using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and performed at the 0.05 significance level.

Results

Although 180 patients were initially recruited into the study, only 154 were included in the final analysis. Fifteen were excluded due to thyroid disease (all hypothyroid on Levothyroxine). The others did not complete the study due to cycle cancelation. Baseline characteristics are shown in Table 1. The mean TSH at first treatment ultrasound was 1.8±1 mIU/L. For the subgroup with positive anti-thyroid antibodies, the mean TSH was 2.3±1.6 mIU/L compared to a mean of 1.7±0.8 mIU/L for antibody-negative subjects (p=0.06).

When E_2 levels rose from a mean minimum of 177.4± 91.9 pmol/L to maximum of 6417.5.0±4300.9 pmol/L during ovarian stimulation, corresponding TSH levels changed from 1.8±1.0 IU/L to a mean of 2.0±1.1 mIU/L. The mean difference in TSH (n=150) was found to be 0.2±0.8 mIU/L (paired t-test p=0.01). Next, when the change in TSH from minimum E2 to the day of pregnancy test was examined, (mean E2 at pregnancy test (n=140) was 2223.4±2062.6 pmol/L and the corresponding TSH at this time point was 2.8±2.1 mIU/L), the mean difference (n=135) was 1.0±2.4 mIU/L (Paired T-test p<0.0001). These results are shown in Table 2.

Table 1 Baseline characteristics of cohort (N=154)

Baseline characteristic	Result (mean, SD or % of cohort)
Age (yrs)	36.6±4.4
Anti-thyroid antibody positive	24 (15.9 %)
Cause of infertility	
-male/tubal factor/endometriosis	85 (55.2 %)
-anovulatory	17 (11.0 %)
-unexplained	52 (33.8 %)
Antral follicle count (n=133)	12.8±8.9
Baseline serum FSH (n=149)	8.1±3.8
Baseline serum E2 (n=138)	225.7±193.4
Baseline serum PRL (n=132)	9.0±6.8
BMI (n=128)	25.0±5.3

Table 2 TSH changes over IVF treatment cycle (N=154)

Time point of interest	Mean ± SD
TSH at minimum E2	
-For entire cohort (n=152)	1.8±1.1
-For antibody-positive (n=24)*	2.3±1.6
-For antibody-negative (n=126)	1.7±0.8
TSH at maximal E2	
-For entire cohort (n=149)	1.9±1.1
-For antibody-positive (n=24)**	2.2±1.6
-For antibody-negative (n=125)	1.9±1.0
TSH at pregnancy test	
-For entire cohort (n=142)	2.8±2.1
-For antibody-positive (n=21)***	2.1±1.0
-For antibody-negative (n=114)	3.0±2.3

*t-test, p=0.06 **t-test, p=0.50, *** t-test, p=0.01

Regression analysis after MI found a significant effect of antibodies, IVF protocol as well as infertility cause (all p-values p=0.01). There was no effect of age, AFC, FSH, BMI, parity, aborta or pregnancy outcome on the change in TSH as defined by "the difference in TSH at maximum and minimum E2". These results are shown in Table 3.

For presence of antibodies we found that the difference in TSH levels are in average smaller by 0.45 units for the positive group than for the negative group. For cause of infertility, "male factor/tubal/endometriosis" had in average a change of 0.35 units smaller than the "unexplained" group. For "IVF protocol" the change was smaller in average for the "long protocol" by 0.32 units as compared to "short protocol". The variable BMI was not found to be a predictor of changes in TSH nor did it predict the main independent variable (presence of anti-thyroid antibodies). Therefore, BMI was included in the MI model as no bias from the estimation of missing BMI values in the final model was expected. The results from the regression using IPW corroborated the results of MI (not shown). In terms of treatment outcomes, positive pregnancy rates (as calculated by positive serum HCG>10 IU/L) were 41 % i.e. 60 out of 145 subjects who underwent embryo transfer had a positive blood test result.

Table 3 Risk factors for change in serum TSH after ART (Maximum likelihood estimation from a multiple linear regression analysis)

Variable of interest	Estimate	Standard Error	T	*P* value
Age	0.02	0.02	1.06	0.29
BMI	−0.01	0.01	−0.85	0.39
Presence of anti-thyroid antibodies	−0.45	0.17	−2.63	0.01
Baseline AFC	0.01	0.01	1.39	0.17
Baseline serum FSH	−0.01	0.02	−0.72	0.47
Cause of infertility Anovulatory	−0.20	0.25	−0.81	0.42
Cause of infertility male factor/tubal/ endometriosis	−0.35	0.14	−2.47	0.01
Protocol (long vs short)	−0.32	0.13	−2.57	0.01
Outcome SAB-ectopic vs positive	−0.12	0.23	−0.52	0.60
Outcome negative vs positive	0.09	0.15	0.56	0.58
Outcome No-HCG vs positive	0.04	0.28	0.16	0.88
Parity status	−0.14	0.18	−0.74	0.46

Discussion

Hypothyroidism is associated with various obstetrical complications such as spontaneous abortion, preeclampsia as well as growth restriction. For this reason, adequate replacement in deficient patients is crucial in terms of lowering these risks and improving fetal neurodevelopment [24]. Although overt hypothyroidism often confers anovulation and sub-fertility, many women with "sub-clinical" hypothyroidism conceive, either spontaneously or through ART (if required for other indications). Despite being clinically euthyroid, such patients might be at risk to become hypothyroid during treatment and therefore might also benefit from replacement therapy. During ART, high E2 levels stimulate Thyroid binding globulin levels that leads to a decrease in free thyroid hormone whereas HCG stimulates the gland. The net effect of high E2 levels on thyroid gland function during in vitro fertilization treatment is largely unknown.

Several authors have studied thyroid function during COH and ART cycles and most have pointed to increased TSH revels. This is, to the best of our knowledge, the largest prospective study of the effects of supra-physiologic serum E2 during ART on TSH levels. We chose to study TSH levels specifically for reasons stated above and also because it is the parameter we use to adjust our replacement doses. The power calculation to show an effect of high E2 on TSH required at least 150 subjects and we met these criteria. All patients undergoing ART were eligible to participate and the authors had no knowledge of their thyroid status at the time of recruitment.

In terms of baseline characteristics, the mean age, ovarian reserve as well as etiology of infertility appeared fairly representative of the patients seen at our center. The cause of infertility was male factor, tubal factor or unexplained in the majority of couples with fewer than 11 % undergoing IVF for anovulatory infertility. This is likely due to the fact that anovulatory patients are treated with ovulation induction, Metformin and/or in-vitro maturation (IVM), prior to undergoing IVF. Given that the mean age of subjects was 37, the mean baseline FSH of 8.4 IU/L and mean baseline E2 of 220 pmol/L appear appropriate. The mean serum TSH in our cohort was 1.8 mIU/L at first ultrasound, which corresponds to mean normal serum levels of 1.5–2.5 mIU/L reported in the literature [2].

In the terms of the applicability of these findings to a general infertility population, the mean age, ovarian reserve tests and etiology of infertility appear to be consistent. However, 16 % of our subjects tested positive for anti-thyroid antibodies. This is higher than the 5–10 % prevalence quoted in the literature for women of reproductive age [24, 28]. This finding might be explained by the fact that infertile women are proposed to have a higher prevalence of thyroid autoimmunity [24].

When the cohort as a whole was studied during controlled ovarian hyperstimulation (COH), there was no clinically significant change in TSH levels as E2 rose (although the difference was statistically significant even at that time point). These results are in keeping with smaller studies by Davis et al. [7] and Reh et al. [27] but contradictory to several others. For example, Alexander et al. prospectively followed 19 patients through pregnancy and found 85 % of their cohort required increased thyroxine beginning early in the first trimester. However, this study involved patients with known thyroid disease whose glands are not able to compensate for E2-induced TBG increases and hence this group was more susceptible to changes in TSH levels. Three patients who underwent assisted reproduction required an even greater dose increase compared to those who conceived naturally [2]. In a recent retrospective study by Poppe et al. in patients with OHSS (and therefore extremely high E2 levels), TSH increased significantly at 2 weeks post-embryo transfer [25]. In addition, patients taking oral estrogen only demonstrated an increase in TSH after 6 weeks of treatment [3]. This points to a time-dependent change in TSH in response to high E2 levels.

In order to determine whether a clinically relevant change in TSH was simply a question of time, we repeated our analysis 2 weeks after oocyte retrieval, on the same day as the pregnancy test. At this time, there *did* appear to be a statistically as well as clinically significant effect of ovarian stimulation on TSH levels, suggesting that the change in TSH takes at least 2 weeks to occur. There was no effect of having a positive versus negative pregnancy test result, suggesting that the effect is a matter of time and not a matter of higher HCG levels (if that were the case, pregnant patients would be expected to have *lower* TSH levels). In our "positive" subjects, the mean HCG level in "pregnant" group was 364 IU/L compared to negative (being<10 mIU/L). These findings are in keeping with those of Gracia et al. [14] who also found higher TSH levels after COH.

The regression model did not show an effect of female age, AFC, BMI, treatment outcome (positive pregnancy or not) nor parity or aborta status. The only variables found to be associated with a significant change in TSH after COH were: anti-thyroid antibodies, cause of infertility and type of protocol. We initially proposed that patients with anti-thyroid antibodies would be more likely to experience a significant change in TSH because they are naturally predisposed to develop hypothyroidism [9]. This is an important consideration given the negative impact of thyroid antibodies on pregnancy outcomes [5, 22, 23].

Muller et al. studied 65 patients with anti-thyroid antibodies and found that TSH increased from a mean 2.3+/−0.3 mIU/L to 3.0 m IU/L after COH ($p<0.0001$) [21]. Although these patients were selected from a previous study performed to assess the impact of anti-thyroid antibodies on miscarriage rates, their findings corroborate ours. However, when we compared the change in TSH between those with and without antibodies, those who were positive actually had a smaller degree of change in their TSH. Contrary to our expectations, these findings suggest antibodies do not confer "susceptibility" during ART cycles. This interpretation must be made with caution, however, as those with antibodies are susceptible to both over and under- functioning of their glands. In fact, Poppe et al. found a more pronounced rise in TSH 20 days after ovarian stimulation in the antibody-positive group compared to those without antibodies. Theirs was a smaller study, however, with only 9 out of 35 patients testing positive for antibodies. Our sub-group involved 24 subjects with positive antibodies but this number is still too small to make any conclusions. Further studies must include an appropriately powered sample size.

We also found that the change in TSH was smaller for those with male/tubal factor compared to unexplained infertility and also smaller in those using the long protocol for COH. One possible explanation is that the group with male/tubal factor represents the same group as those receiving the long protocol. Importantly, those with male/tubal factor infertility have less risk of underlying autoimmune or endocrine abnormalities compared to those with unexplained infertility.

One limitation of our study was that we did not follow free T4 levels throughout the treatment (although we did ensure that all serum levels were in normal range prior to commencing treatment) nor did we trace changes in antibody levels. This data would be interesting for future study in terms of understanding fluctuations of gland function during treatment. However, we feel that the data presented is sufficient to show that thyroid function is affected by ART treatment.

Our results suggest that, although TSH does not change significantly during the course of IVF treatment, there is a clinically and statistically significant rise detectable by the time of pregnancy test. This is particularly important in certain "at risk" sub-groups such as those with anti-thyroid antibodies and those patients with "borderline" high TSH values pre-treatment and in whom we might consider levothyroxine prior to ART. For this reason, patients with TSH levels already above the "ideal" 2.5 mIU/L at the beginning of ovarian stimulation should be retested approximately 2 weeks after treatment especially those with antibodies, male or tubal factor infertility or those undergoing the long protocol for ovarian stimulation. We propose that this should be done at the same time as the pregnancy test in

order to immediately identify those patients requiring replacement if pregnancy ensues. Given the minimal risk of thyroid hormone replacement and the significant advantages in terms of reducing miscarriage rates as well as fetal neurodevelopment, a low threshold for giving additional thyroid hormones should be considered during pre-conception and early pregnancy.

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