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Incidence of elevation of serum thyroid-stimulating hormone during controlled ovarian hyperstimulation for in vitro fertilization

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ABSTRACT

Objective: To evaluate the rate of euthyroid women encountering an elevation of serum TSH above the threshold of 2.5 mIU/L during controlled ovarian hyperstimulation (COH) for IVF.
Study design: Six-month prospective cohort study on 175 consecutive euthyroid women undergoing their first IVF cycle. Serum TSH assessments were performed before COH, at the time of hCG administration and at +16 days after hCG administration. Women were eligible if serum TSH tested the month preceding the IVF cycle was 0.4–2.5 mIU/L. A history of thyroid disorders was an exclusion criterion.
Results: Serum concentrations of TSH at the three scheduled assessments were 1.5 ± 0.5, 2.2 ± 1.0 and 2.1 ± 1.1 mIU/L, respectively. A statistically significant increase occurred between basal levels and levels at the time of hCG administration ($p < 0.001$). Afterwards, levels remained stable ($p = 0.49$). Serum TSH at the time of hCG administration exceeded the threshold of 2.5 mIU/L in 61 subjects, corresponding to 35% (95%CI: 28–42%). At +16 days after hCG administration, this event was observed in 47 subjects (27%, 95%CI: 21–34%). Baseline characteristics of women who did and did not exceed the threshold were similar apart from basal serum TSH, which was higher in the former group. The OR was 7.6 (95%CI: 2.9–20.2) per mIU/L ($p < 0.001$). Cycle outcome and pregnancy rate were also similar.
Conclusion: Serum TSH exceeds the threshold of 2.5 mIU/L during COH in one out of three women who are euthyroid prior to enter an IVF cycle. Further evidence is warranted to elucidate the clinical relevance of our findings.

1. Introduction

Optimal thyroid function is necessary to ensure normal fertility. Women with hypothyroidism are at increased risk of menstrual disorders and infertility [1]. Moreover, maternal hypothyroidism in pregnancy has been associated with miscarriage, preterm birth and reduced cognitive function in offspring [2] and most guidelines now recommend the testing of thyroid function in pregnancy at least in women at increased risk [3–6,18].

An emerging concern in the field of reproductive medicine is the impact of controlled ovarian simulation (COH) on thyroid function [7]. There is some evidence that serum TSH increases during COH but data are equivocal. In a recent review on this topic, Mintziori et al. [7] identified three studies reporting significant increase of TSH during COH (one during COH and two within one month after COH) [8–10], two studies failing to document significant change [11,12] and one study reporting an increase only in cycles in which pregnancy was achieved [13]. More recently, Gracia et al. added further evidence on a possible detrimental effect of COH. They reported that the serum concentration of TSH exceeded the threshold of 2.5 mIU/L during or after COH in 22 out of 50 women (44%) with basal normal thyroid function [14].

The present study was designed to further investigate the influence of COH on serum TSH in women undergoing IVF-ICSI cycles. The primary aim was to determine the rate of women with basal TSH levels ranging 0.4–2.5 mIU/L whose serum TSH levels exceeded 2.5 mIU/L during COH. Secondary aims included the investigation of factors associated with this condition and its impact on the chances of pregnancy.

2. Materials and methods

Patients who were selected for IVF between January 2011 and June 2011 at the Infertility Unit of the Fondazione Cà Granda

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Ospedale Maggiore Policlinico were considered for study entry. Women were eligible as cases if serum TSH tested the month preceding the IVF cycle was 0.4–2.5 mIU/L [15]. Women with serum TSH exceeding 2.5 mIU/L were excluded. Additional inclusion criteria were as follows: (1) no previous IVF cycles, (2) no history of thyroid disorders, (3) regular menstrual cycles, and (4) serum day 3 FSH $<$ 12 IU/ml and AMH $>$ 0.5 ng/ml. Women whose treatment was cancelled during the stimulation and those who did not undergo embryo transfer were subsequently excluded. The local Institutional Review Board approved the study and all recruited patients signed an informed consent.

All patients underwent transvaginal ultrasound between Day 1 and Day 8 of the cycle during the month preceding the beginning of hyperstimulation. Serum TSH was tested at this time. Patients were monitored and managed according to a standardized clinical protocol as reported elsewhere [16]. Briefly, the protocol of stimulation and the dose-type of recombinant FSH (Gonal-F®, Merck Serono, UK) were determined on an individual basis according to the characteristics of the patients, such as age, serum hormonal levels and antral follicle count. Patients underwent serial transvaginal ultrasound and hormonal monitoring during hyperstimulation. When three or more leading follicles with a mean diameter $>$ 18 mm were visualized, 250 μg of recombinant hCG (Ovitrelle®, Merck Serono, UK) was administered s.c. The second serum TSH assessment was done on the same day but before the administration of recombinant hCG. Oocyte retrieval was performed transvaginally 36 h after the hCG injection. Embryo transfer was performed 48–72 h after the oocyte collection. Cycles were cancelled if there was a poor or hyper-response. We defined hyper-response as a serum estradiol concentration $>$4000 pg/ml and/or more than 20 follicles identified on ultrasound scan before hCG administration. Poor response was defined by echographic evidence of fewer than three follicles during ovarian hyperstimulation. Serum hCG assessment to ascertain the development of pregnancy was performed at +16 days from hCG administration. The third serum TSH was scheduled on the same day. Clinical pregnancy was defined as the ultrasonographic demonstration of a live embryo within an intrauterine gestational sac 4–5 weeks after embryo transfer. The implantation rate was calculated as the ratio between the number of gestational sacs identified at this time and the number of embryos transferred. Women whose serum TSH exceeded 2.5 UI/L at +16 days after hCG administration were referred after the US ascertainment of pregnancy to the endocrinologist for further thyroid function evaluation and to initiate levothyroxine treatment if needed. TSH assays were measured with the Immulite analyzer, a fully automated solid-phase third generation immunoassay analyzer with a chemiluminescent detection system (Diagnostic Products Corp.). The intra and inter-assay coefficients of variation were both $<$ 10%.

Data analysis was performed using the Statistics Package for Social Sciences (SPSS 18.0, Chicago, IL, USA). Data were compared using Student's *t* test, Wilcoxon test for unpaired data or Fisher's exact test, as appropriate. The main outcome chosen was the rate of women whose serum TSH exceeded 2.5 UI/L at the time of hCG administration. The sample size was calculated stating as clinically relevant a rate of women fulfilling this criteria of about 30%. On these bases and setting type I and II errors at 0.05 and 0.20, respectively, the required sample size consisted of about 180 women. In searching for variables associated with the outcome, we considered as statistically significant a p value below 0.05. A logistic regression model was used to control for confounders. In this regression model, stepwise forward algorithms were performed to select variables at a p-value cut-off of 0.05. The goodness-of-fit of the model was assessed by calculating Nagelkerke's R^2. Receiver operating characteristic (ROC) curve was performed to analyze model performance.

3. Results

One hundred and seventy-five women met our selection criteria. All women underwent the three scheduled assessments. The mean ± SD age and BMI of the cohort were 35.8 ± 3.8 years and 21.8 ± 2.8 kg/m^2, respectively. Twenty-four women (14%) had previous pregnancies. Indications for IVF-ICSI were as follows: male factor (n = 61, 35%), endometriosis (n = 43, 25%), tubal factor (n = 19, 11%), unexplained (n = 22, 13%) and mixed (n = 30, 17%). For COH, the long protocol, the short protocol and the protocol with GnRH antagonists were used in 98 (56%), 27 (15%) and 50 (29%) cases, respectively. The mean ± SD total dosage of gonadotropins used and serum levels of estradiol at the time of hCG administration were 2671 ± 1268 IU and 2021 ± 1081 pg/ml, respectively. The mean number of oocytes retrieved was 8.4 ± 4.3, the mean number of embryos transferred was 2.0 ± 0.5 and the total number of clinical pregnancies was 52 (30%). No ectopic pregnancies were observed.

Serum levels of TSH at basal assessment, at the time of hCG administration and at +16 days after hCG administration were 1.5 ± 0.5, 2.2 ± 1.0 and 2.1 ± 1.1 mIU/L, respectively. A statistically significant increase occurred between basal levels and levels at the time of hCG administration ($p < 0.001$). Afterwards, levels remained stable (p = 0.49). This result is illustrated in Fig. 1. The median (5th–95th percentiles) levels at the three time points were 1.6 (0.6–2.4), 2.1 (0.8–3.8) and 1.9 (0.7–4.3) mIU/L, respectively. At the time of hCG administration, serum TSH level was higher than the baseline in 151 out of 175 patients (86.3%) whereas it was lower or unchanged in the remaining 24 women (13.7%). Comparing serum TSH levels of third blood sample with those of the second, serum TSH was increased in 78 (44.6%) and decreased or unchanged in 97 (55.4%) women. Finally, comparing the results of the last blood sample with those of the baseline sample, serum TSH values were increased in 135 (77.1%) and decreased or unchanged in 40 (22.9%) women.

Serum TSH at the time of hCG administration exceeded the threshold of 2.5 mIU/L in 61 subjects, corresponding to 35% (95%CI: 28–42%). At +16 days after hCG administration, this event was observed in 47 subjects (27%, 95%CI: 21–34%). In none of the studied cases was serum TSH below 0.4 mIU/L at the time of hCG administration (0%, 95%CI: 0–2%). This event occurred in one pregnant woman at +16 after hCG administration (0.6%, 95%CI: 0.02–3%).

Baseline characteristics and cycle outcome of women whose serum TSH did and did not exceed the threshold of 2.5 mIU/L at the time of hCG administration are shown in Tables 1 and 2. Only basal serum TSH concentration significantly differed between the study

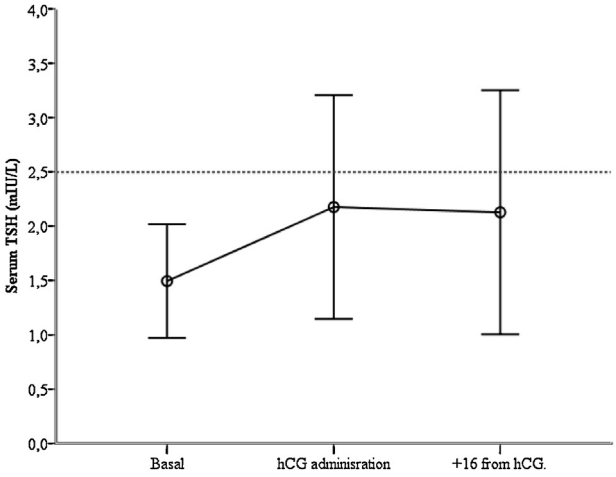

Fig. 1. Serum levels of TSH at basal assessment, at the end of the treatment with recombinant FSH (just before hCG administration) and at +16 days after hCG administration. *$p < 0.001$ when compared to basal assessment.