Decrease of Free Thyroxine Levels after Controlled Ovarian Hyperstimulation*

A. F. MULLER, A. VERHOEFF, M. J. MANTEL, F. H. DE JONG, AND A. BERGHOUT

Departments of Internal Medicine (A.F.M., A.B.), Obstetrics and Gynecology (A.V.), and Clinical Chemistry (M.J.M.), Zuidzijdsziekenhuis Rotterdam, 3075 EA Rotterdam, The Netherlands; and Department of Internal Medicine III, University Hospital Dijkzigt (F.H.d.J.), 3015 GD Rotterdam, The Netherlands

ABSTRACT

Controlled ovarian hyperstimulation could lead to opposing effects on thyroid function. Therefore, in a prospective study of 65 women undergoing controlled ovarian hyperstimulation, thyroid hormones, T4-binding globulin, TPO antibodies, gonadotropins, estradiol, and PRL were measured before and after controlled ovarian hyperstimulation.

After ovarian stimulation (mean ± se of mean): free T4 decreased, 14.4 ± 0.2 vs. 12.9 ± 0.2 pmol/L (P < 0.0001); thyroid-stimulating hormone increased, 2.3 ± 0.3 vs. 3.0 ± 0.4 mU/L (P < 0.0001); T4-binding globulin increased, 25.2 ± 0.7 vs. 33.9 ± 0.9 mg/L (P < 0.0001); total T4 increased, 98.1 ± 2.3 vs. 114.6 ± 2.5 nmol/L (P < 0.0001); total T3 increased, 2.0 ± 0.04 vs. 2.3 ± 0.07 nmol/L (P < 0.0001); TPO antibodies decreased, 370 ± 233 U/mL vs. 355 ± 224 U/mL (P < 0.0001); LH decreased, 8.1 ± 1.1 vs. 0.4 ± 0.1 U/L (P < 0.0001); FSH did not change, 6.5 ± 0.6 vs. 7.9 ± 0.9 U/L (P = 0.08); human CG increased, <2 ± 0.0 vs. 195 ± 16 U/L (P < 0.0001); estradiol increased, 359.3 ± 25.9 pmol/L vs. 349.1 ± 298.3 pmol/L (P < 0.0001); and PRL increased, 0.23 ± 0.02 vs. 0.95 ± 0.06 U/L (P < 0.0001).

Because low maternal free T4 and elevated maternal thyroid-stimulating hormone levels during early gestation have been reported to be associated with impaired psychomotor development in the offspring, our findings indicate the need for additional studies in the children of women who where exposed to high levels of estrogens around the time of conception. (J Clin Endocrinol Metab 85: 545–548, 2000)

Low Maternal free T4 (fT4) levels during early gestation are associated with impaired psychomotor development in infancy, persisting into childhood (1, 2).

During pregnancy, high estradiol (E2) levels lead, through a rise in T4-binding globulin (TBG), to a transient drop in fT4 levels (3–5). Human CG (hCG) is known to exert a thyrotrophic action both in vitro and in vivo, best explained by the structural homology of thyroid-stimulating hormone (TSH) and hCG and their respective receptors (6). This explains why serum TSH does not rise during the first trimester but decreases reciprocally with the increase in hCG (5). Controlled ovarian hyperstimulation—for conventional in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)—could, therefore, lead to opposing effects on thyroid function: the thyrotrophic action of hCG could result in elevated fT4 levels; alternatively, the induced rise in E2 could lead to a lowering of fT4.

The aim of the present study was to determine the acute effects of controlled ovarian hyperstimulation on thyroid function. We, therefore, designed a prospective study of women undergoing controlled ovarian hyperstimulation.

Materials and Methods

We studied 65 of 177 women who previously participated in a prospective study on thyroid autoimmunity and abortion (7). The study was approved by the hospital ethics committee, and all subjects gave informed consent at initial presentation.

Our IVF program has been described in detail previously (8). Ovarian stimulation consisted of a 1-mg GnRH-analog sc or intranasally from cycle day 1 to days 10–12, 225 IU human menopausal gonadotrophin (hMG) im from day 3 to days 9–11, and 10,000 IU hCG im 35 h before follicle puncture. Follicle growth was assessed by ultrasound from day 10. Follicle puncture was done on day 14 in the majority of women. There was no difference in controlled ovarian hyperstimulation in those receiving ICSI and conventional IVF. Blood was drawn at random during the menstrual cycle from all women at their initial visit and after ovulation induction immediately before or after transvaginal follicle puncture. After the initial visit, TSH was determined immediately, whereas all other assays were done from frozen samples (−70 C).

To investigate assay cross-reactivity, one ampoule hMG (75,000 U/L) was diluted in saline to 75 U/L. In this solution TSH and hCG were measured.

Assays

TSH, total T4, fT4, FSH, LH, hCG (total and B), and PRL were determined with an immunoluminometric assay (Chiron Corp., East Walpole, MA). Reference ranges were: TSH, 0.2–4.5 mU/L; total T4, 1.3–2.8 nmol/L; fT4, 9–22 pmol/L; and PRL, 0.03–0.63 U/L. Total T4 was determined with an in-house RIA with a reference range of 64–132 nmol/L. TBG was determined with a RIA (Brahms, Berlin, Germany). Estradiol was determined with a RIA (Diagnostic Product Corporation, Los Angeles, CA). TPO antibodies were determined with a RIA (Henning Berlin GmbH & Co., Berlin, Germany).

Statistics

Qualitative data between groups were tested using the χ2 test. Data on hormones and antibodies were analyzed by the Wilcoxon matched-pairs signed-ranks test; correlations are given as Spearman’s rank correlation coefficient (all P values are two-sided). P values of less than 0.05 were considered significant. Data are presented as mean ± se of mean.
Results

General data

There were no differences in age, cause of infertility, thyroid function, family history of thyroid disease, smoking behavior (Table 1), number of previous pregnancies and deliveries or spontaneous abortions between study subjects and those who did not consent to repeated blood sampling (nonparticipants). None of the study subjects used thyroid medication.

Thyroid function and TPO antibodies

After ovarian stimulation: fT4 decreased, (before vs. after) 14.4 ± 0.2 pmol/L vs. 12.9 ± 0.2 pmol/L (P < 0.0001) (Fig. 1); total T4 increased, 98.1 ± 2.3 nmol/L vs. 114.6 ± 2.5 nmol/L (P < 0.0001); total T3 increased, 2.3 ± 0.2 pmol/L vs. 2.3 ± 0.2 pmol/L (P < 0.0001); TBG increased, 25.2 ± 0.7 mg/L vs. 33.9 ± 0.9 mg/L (P < 0.0001); TSH increased, 2.3 ± 0.3 pmol/L vs. 3.0 ± 0.4 pmol/L (P < 0.0001) (Fig. 2); and TPO antibodies decreased, 370 ± 233 U/mL vs. 355 ± 224 U/mL (median, 57 U/mL and 44 U/mL, respectively) (P < 0.0001).

In those women receiving ICSI, fT4 was slightly, but significantly, higher after ovarian hyperstimulation compared with women receiving conventional IVF: 13.7 ± 0.4 pmol/L vs. 12.6 ± 0.3 pmol/L (P < 0.05).

Gonadotropins, E2, and PRL

After ovarian stimulation: LH decreased, 8.1 ± 1.1 U/L vs. 0.4 ± 0.1 U/L (P < 0.0001); FSH did not change, 6.5 ± 0.6 U/L vs. 7.9 ± 0.9 U/L (P = 0.08); E2 increased, 359.3 ± 25.9 pmol/L vs. 3491.8 ± 298.3 pmol/L (P < 0.0001); hCG increased, less than 2 ± 0.0 U/L vs. 195 ± 16 U/L (P < 0.0001); and PRL increased: 0.23 ± 0.02 U/L vs. 0.95 ± 0.06 U/L (P < 0.0001).

Correlations

A significant correlation exists between the increase in E2 and the increase in TBG (Fig. 3) and total T4; r = 0.50, P < 0.0001 and r = 0.73, P < 0.0001, respectively. The increase in TBG was significantly correlated with the decrease in fT4, r = −0.26, P < 0.05 (Fig. 4).

Assay cross-reactivity

In the saline containing 75 U/L FSH and LH (hMG), TSH and hCG levels were, respectively, 0.02 mU/L and 12 U/L, indicating that the gonadotropins did not contribute significantly to the levels of TSH and hCG estimated after ovulation induction.

Discussion

In this prospective study, we found controlled ovarian hyperstimulation to lead to a lowering of fT4 levels concom-

![Fig. 1. fT4 levels before and after ovarian stimulation.](image-url)
tant with a rise in TSH, indicating decreased T₄ availability at the tissue level at the time of follicle puncture. This increase in TSH is in contrast with the generally observed decrease in TSH during the first trimester of pregnancy (3–5). The possible significance of these findings lies in the recently described association between maternal thyroid status and subsequent neuropsychological development of the child (1, 2). Pop et al. (1) found fT₄ levels within the lowest 10th percentile at 12 weeks gestation in apparently healthy women to be associated with impaired psychomotor development at 10 months of age in their offspring. That these differences persist into childhood has very recently been shown by Haddow et al. (2), who provide evidence that children born from mothers with hypothyroidism during the second trimester of pregnancy have lower IQ scores and more school problems at 7–9 yr of age than children born from mothers who were euthyroid during pregnancy. These studies provide compelling evidence that even relatively mild disturbances in maternal thyroid function can lead to persistent and clinically relevant impairment in neuropsychological performance.

Animal, as well as human, studies have shown that due to the inability of the fetal thyroid to produce thyroid hormone during early pregnancy the maturing brain is totally dependent on maternal supply of thyroid hormone (9–12), thus, offering an explanation for the association between low maternal fT₄ levels and impaired psychomotor development in the offspring.

Ovarian hyperstimulation leads to hyperestrogenism, which in turn leads to increased TBG levels (for review see Ref. 3) and, therefore, to a decrease in fT₄ (3). During early pregnancy, some degree of thyroid stimulation by hCG exists; in some women this can give rise to gestational hyperthyroidism (3, 6). In molar pregnancy or chorionic carcinoma severe hyperthyroidism may even be the presenting symptom (6, 13, 14). Apparently, the hCG administration as applied during ovarian hyperstimulation is too short and/or too low-dosed to counterbalance the opposing effect of increased T₄ binding.

It might be argued that thyroid function at baseline was influenced by the phase of the menstrual cycle. However, it has been shown previously that thyroid function is unchanged during the follicular and luteal phases (5). Another possible source of bias could be assay interference. However, we found only negligible cross-reactivity. Moreover, during ovarian hyperstimulation, PRL (a polypeptide hormone) increased significantly and this change was near significantly correlated with the rise in TSH (a glycoprotein hormone); r = 0.22, P = 0.09, indicating a pituitary source of TSH and not assay cross-reactivity. Finally, we only measured TBG, whereas albumin and transthyretin can bind T₄ as well. However, during pregnancy the fraction of T₄ bound by TBG increases to more than 75%, as compared to two thirds in a
nonpregnant state (3). In addition, concomitantly with the rise in TBG, total T4 levels—measuring all bound T4—increased as well.

There is strong evidence that sex steroids can modulate Th1/Th2 cytokine balance in such a way that during pregnancy cell-mediated immune function and Th1 cytokine production are suppressed and humoral immunity and Th2 cytokine production are enhanced (15, 16). The significant decline in TPO titers argues against a role of thyroid autoimmunity in the lowering of fT4 levels during controlled ovarian hyperstimulation.

In several studies (17–22), no difference in the developmental outcome in children conceived by conventional IVF compared with non-IVF controls was found. However, in none of these studies maternal fT4 levels in early gestation were taken into consideration. When comparing children conceived by ICSI (25% of our study subjects underwent ICSI) with children conceived by conventional IVF, there is an increased risk of developmental delay at 1 yr of age in children conceived by ICSI (23). In our study, we found fT4 levels after ovarian hyperstimulation to be slightly higher in women who subsequently underwent ICSI compared with those who underwent conventional IVF.

In conclusion, we have found that ovarian hyperstimulation leads to a lowering of fT4 levels with a concomitant rise in TSH. These findings have potential implications for women whose fT4 levels are already in the lower range of TSH. These findings have potential implications for the development in the offspring of women undergoing controlled ovarian hyperstimulation.

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