Serum Prolactin and TSH in an In Vitro Fertilization Population: Is There a Link Between Fertilization and Thyroid Function?

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Purpose: Measurements of TSH and prolactin are generally included in the evaluation of female infertility, but their value in women coming to in vitro fertilization (IVF) has been questioned.

Methods: In this study, we sought to investigate whether prolactin or TSH, measured in 509 specimens collected prior to therapy, predicted outcome in a prospective study of couples undergoing IVF between 1994 and 2001.

Results: TSH was higher in women whose fertility problem was attributed to a male factor, and prolactin was lower if the measurement was taken during menses. TSH and prolactin were positively correlated (p < 0.0001). Neither TSH nor prolactin levels correlated with overall IVF outcome; however, TSH levels were significantly higher among women who produced oocytes that failed to be fertilized and this finding persisted after adjustment for several co-variates, including sperm motility. Among women who had at least one oocyte inseminated, the likelihood that they would have fewer than 50% of their eggs fertilized was significantly related to higher TSH levels in a multivariate model.

Conclusion: We conclude that TSH may predict poor fertilization in IVF and reflect the importance of thyroid hormones in oocyte physiology.

KEY WORDS: Fertilization; IVF; oocytes; prolactin; TSH.

INTRODUCTION

Traditionally, measurements of prolactin and TSH have been considered important components of the evaluation of women presenting with infertility. In a survey of reproductive endocrinologists in the United States, more than half indicated that they “always” or “almost always” ordered TSH and prolactin to evaluate the endocrine status of their patients (1). However, the value of routine endocrine testing in an infertility population (2) and especially an in vitro fertilization (IVF) population has been questioned (3,4). In this study we sought to identify whether IVF outcomes were associated with pretreatment IVF and prolactin measured in archived blood specimens from women seeking IVF.

Patients and Methods

Since 1994, we have been studying couples undergoing assisted reproductive technology (ART) at 1 Ob-Gyn Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, 221 Longwood Avenue, Brigham and Women’s Hospital, Boston, Massachusetts 02115. 2 Reproductive Endocrinology Unit Laboratory, Department of Obstetrics and Gynecology, Fruit Street Massachusetts General Hospital, Boston, Massachusetts. 3 Boston IVF, Waltham, Massachusetts. 4 Reproductive Science Center, Deaconess-Waltham Hospital, Waltham, Massachusetts. 5 Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women’s Hospital, Boston, Massachusetts. 6 To whom correspondence should be addressed; e-mail: dcramer@partners.org.
three IVF clinics in greater Boston (Boston IVF, the Brigham and Women’s IVF Program, and the Reproductive Science Center of Boston) under protocols approved by the Brigham and Women’s Hospital Human Research Committee. The study has had two funding phases—the first operating between August 1994 and March 1998 and the second beginning January, 1999 and still ongoing. During both phases, we used self-administered questionnaires to obtain information on epidemiologic variables and abstracted details on treatment and outcome from clinic records. Treatment details included description of the controlled ovarian stimulation regimen that involved gonadotropin releasing hormone agonists used in short or long regimens and gonadotropins, either human menopausal or recombinant, as well as details related to retrieval, fertilization, and embryo transfer. Because we sought to identify epidemiologic characteristics of the couple that might predict IVF success, we excluded couples who required either donor eggs or semen and those serving as gestational carriers.

We also sought to obtain a variety of specimens in the women agreeing to be studied. This included, when possible, a basal blood specimen measured sometime during days 1 through 5 of a menstrual cycle prior to any use of hormones. For women in whom it was not possible to obtain a blood specimen timed to the menses, we sought to obtain a specimen before treatment was begun. The former specimens were called “true baseline” and the latter “initial” specimens. Additionally, we retrieved sera from bloods obtained during the course of ovarian stimulation, follicular fluid at the time of oocyte retrieval, and a luteal phase blood specimen. All specimens were processed, aliquoted, and stored at −80°C.

Approximately 65% of subjects approached in the first phase of the study agreed to participate and 1244 couples were enrolled. In the second phase of the study, 67% of couples approached agreed to participate and 974 had been enrolled as of July 2001. For the current investigation, we focused on women who had either a true baseline or an initial specimen obtained prior to any treatment and whose outcome for at least the first cycle of IVF was known. This yielded a total of 313 women from study 1 and 196 from study 2 with pretreatment specimens (true baseline or initial). In these 509 women, 44.8% were known to have had a prior TSH measurement and 38.5% were known to have had a prior prolactin measured prior to enrollment.

Prolactin and TSH were measured in serum using the AxSYM Immunoassay system (Abbott Diagnostics, Chicago, IL). Both tests are solid-phase double antibody enzyme immunoassays employing microparticle enzyme immunoassay (MEIA) technology. Prolactin, captured by a monoclonal mouse antibody attached to microparticles, is measured by a rabbit antibody conjugated to alkaline phosphatase. This assay has no detectable cross-reactivity with FSH, LH, TSH, or hCG, <0.01% cross-reactivity with human Placental Lactogen and <1.7% cross-reactivity with hGH. Prolactin levels in serum were quantified (ng/mL) on the basis of the assay calibrators standardized using the World Health Organization 3rd International Standard (WHO 3rd IS 84/500; 1 ng = 24 μIU). The limit of detection (e.g., the lowest measurable concentration of prolactin in serum that can be distinguished from zero) was 0.6 ng/mL. The working range of the assay was from 0.6 to 200 ng/mL and performance of the assay was monitored using three quality control sera (Abbott Diagnostics). The mean concentrations of prolactin in control sera were 7.0, 17.6, and 34.8 ng/mL, and the CVs were 8.3, 6.8, and 4.8%, respectively.

Human TSH was also measured in serum by using the MEIA technology (Ultrasensitive hTSH II). TSH, captured by a monoclonal mouse antibody attached to microparticles, is measured by a goat antibody conjugated to alkaline phosphatase. This assay has <0.001% cross-reactivity with FSH and <0.0001% cross-reactivity with LH or hCG. TSH levels in serum were quantified (μIU/mL) on the basis of assay calibrators standardized using the World Health Organization TSH 80/558. The limit of detection (e.g., the lowest measurable concentration of TSH in serum that can be distinguished from zero) was 0.03 μIU/mL. The functional sensitivity (concentration of hTSH that can be measured with an interassay CV of 20%) was 0.06 μIU/mL. The working range of the assay was from 0.1 to 100 μIU/mL. Performance was monitored using three quality control sera (Abbott Diagnostics). The mean concentrations of hTSH in the controls were 0.26, 6.14, and 29.72 μIU/mL, and the CVs were 7.1, 6.2, and 7.4%, respectively.

Means and standard deviations for TSH and prolactin were examined in subjects categorized by various baseline characteristics as well as categorical outcomes including whether a clinical pregnancy was achieved, at what point failure during the IVF process may have occurred, or by average or below average oocyte fertilization. We chose to focus on first cycle results because this would yield the outcomes closest in time to when the pretreatment blood had been drawn. Differences among women by level of TSH or prolactin for particular characteristics were assessed by using three quality control sera (Abbott Diagnostics). The mean concentrations of prolactin in control sera were 7.0, 17.6, and 34.8 ng/mL, and the CVs were 8.3, 6.8, and 4.8%, respectively.

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