Serum Progesterone Concentrations on the Day After Human Chorionic Gonadotropin Administration and Progesterone/Oocyte Ratios Predict in Vitro Fertilization/Embryo Transfer Outcome

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Purpose: In gonadotropin-releasing hormone analogue-pretreated in vitro fertilization−embryo transfer cycles, pregnancy rates are inversely related to serum progesterone levels on the day of administration of human chorionic gonadotropin. The relationship of the progesterone concentration on other days in the periovulatory period to pregnancy rates in such cycles is little studied. We therefore retrospectively analyzed the relationship between progesterone concentrations on the day after human chorionic gonadotropin and pregnancy in 114 cycles, 28 and 23 of which produced clinical and ongoing/delivered pregnancies, respectively. To assess the effect of the extent of follicular luteinization on success, we also studied the relationship between the progesterone concentration per oocyte retrieved and pregnancy for the day of and day after human chorionic gonadotropin.

Results: Progesterone concentrations on the day after human chorionic gonadotropin were inversely associated with clinical pregnancy by multiple logistic regression analysis (P < 0.05). Progesterone/oocyte ratios were inversely associated with clinical pregnancy (P < 0.05) and ongoing/delivered pregnancy (P < 0.02) for both the day of and the day after human chorionic gonadotropin.

Conclusion: The study results extend the window of time during which elevated progesterone concentration is associated with poor outcome to at least 2 days. This finding is consistent with hypothetical mechanisms attributing the link between progesterone concentration and outcome to either endometrial or follicle/oocyte events. The association of lack of follicular luteinization (low progesterone per oocyte ratios) and favorable outcome suggests a predominant effect of progesterone on follicle/oocyte quality. Further studies are needed to clarify the mechanisms underlying the association between progesterone and in vitro fertilization−embryo transfer outcome.

KEY WORDS: serum progesterone; day after human chorionic gonadotropin administration; progesterone/oocyte ratio; in vitro fertilization; pregnancy rate.

INTRODUCTION

In vitro fertilization−embryo transfer (IVF-ET) pregnancy rates have frequently been reported to be inversely related to serum progesterone (P₄) levels on the day of administration of human chorionic gonadotropin (hCG) (1−8). In five of these studies (4−8), the most common (9) and most successful (10) regimen of ovarian stimulation in current use, gonadotropin-releasing hormone (GnRH) analogue desensitization followed by gonadotropin stimulation, was employed. Thus, the relationship between
serum \(P_4\) on the day of hCG and IVF-ET success is of utmost relevance to the current and foreseeable future practice of IVF-ET.

Although a significant inverse relationship between serum \(P_4\) on the day of hCG and the success of IVF-ET is established in many programs, the endocrinologic mechanism underlying the relationship is unclear. In the study by Silverberg et al. (5), 0 of 14 patients with elevated \(P_4\) levels \(>0.9\) ng/ml conceived in their “fresh” transfer cycle; 2 of the patients subsequently established normal pregnancies, with cryopreserved embryos conceived in their elevated \(P_4\) cycles. Based on this finding, the authors suggested that the mechanism of the deleterious effect of an elevated \(P_4\) was abnormally accelerated endometrial maturation leading to impaired endometrial receptivity. In the study by Schoolcraft et al. (4), higher \(P_4\) levels were associated with higher human menopausal gonadotropin doses and diminution of the estradiol \(E_2\) rise on the day after hCG administration. These observations were interpreted by the authors as suggesting that elevated \(P_4\) was a marker of impaired follicle/oocyte quality due to postmaturity. Currently the controversy over the mechanism of action of increased \(P_4\) secretion on the day of hCG in IVF-ET remains unresolved.

To further our understanding of the effect and mechanism of action of serum \(P_4\) on IVF-ET success, we retrospectively studied the relationship between serum \(P_4\) concentrations on the day after hCG administration and IVF-ET success in GnRH analogue pretreated cycles. Intuitively, it seems plausible that the longer a significant difference in \(P_4\) between successful and unsuccessful cycles exists, the more likely it is that the effect is exerted on the endometrium; conversely, the more transient the difference, the greater is the likelihood that the effect is on follicle/oocyte. Although \(P_4\) levels on the day after hCG have been studied in cycles not treated with GnRH analogues (2,11), very few studies have been performed in GnRH analogue-treated cycles.

**MATERIALS AND METHODS**

Stored frozen sera drawn on the day after administration of hCG from 114 cycles in 91 patients in our IVF-ET program were available for determination of \(P_4\) concentration. All patients studied were less than 40 years old, were down-regulated with a GnRH analogue prior to the initiation of ovarian stimulation, and had normal fertilization of at least one oocyte, permitting “fresh” zygote or embryo transfer.

The usual clinical protocol utilized for IVF-ET was as follows. Leuprolide acetate (LA), 1.0 mg/day, subcutaneously, was initiated on approximately postovulatory day 10. After subsequent menses, on cycle day 2 or 3, baseline transvaginal ultrasound (U/S) was performed. If baseline U/S showed no ovarian sonolucencies greater than 14 mm, ovarian stimulation was initiated. Patients with larger sonolucencies were continued on LA, 1.0 mg/day, for 2 to 10 days until the sonolucency collapsed or was aspirated transvaginally. Ovarian stimulation was initiated with human menopausal gonadotropins (hMG), 300 IU/day intramuscularly for 3 days; contemporaneously, LA was reduced to 0.5 mg/day. Serum estradiol \(E_2\) and U/S were obtained on the morning of the fourth day of hMG stimulation; subsequent hMG dosage and timing of U/S and \(E_2\) monitoring were individualized according to patient response. Human chorionic gonadotropin, 10,000 IU intramuscularly, was administered and LA discontinued when at least two follicles reached 16 mm or greater in mean diameter (two perpendicular measurements, transverse plane), and serum \(E_2\) was greater than 250 pg/ml per follicle \(\geq 16\) mm. Serum samples were drawn between 0730 and 1000 hr and stored, after completion of clinical same-day \(E_2\) assay, at \(-20^\circ\)C. Ultrasound-guided transvaginal follicle aspiration was performed 34 to 35 hr after administration of hCG. Pronuclear-stage uterine embryo transfer was performed approximately 24 hr after retrieval; generally, three or four pronuclear-stage embryos were transferred. The luteal phase was supported with \(P_4\) in oil, 25 mg/day intramuscularly, beginning on the day of transfer and continuing to the day of pregnancy testing. Qualitative serum pregnancy test was performed on the 12th day after transfer. Transvaginal U/S was performed 4 to 5 weeks after embryo transfer to assess fetal viability. Clinical pregnancy was defined as the documentation with U/S of an intrauterine gestational sac or the presence of chorionic villi in uterine curettings. In preclinical pregnancy, hCG was detected on the day of pregnancy testing, but menstrual bleeding ensued prior to the time of pregnancy U/S.

Serum \(E_2\) was measured by a direct, solid-phase radioimmunoassay (RIA) (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA) performed according to manufacturer’s instructions, including