Timing of Progesterone Rise Around a Surge in Endogenous Luteinizing Hormone or the Injection of Human Chorionic Gonadotropin in Controlled Ovarian Stimulation for in Vitro Fertilization

INTRODUCTION

In the controlled ovarian hyperstimulation induced for in vitro fertilization (IVF), the ultimate goal is to obtain multiple mature oocytes which can develop to term pregnancy. It has been reported that the final maturation of oocytes and the outcome of IVF are greatly influenced by a surge in endogenous luteinizing hormone (LH) and by an elevation of progesterone (P) level (1). However, Lejeune et al. (2) suggest that when the LH rise is untimely, one should not attempt laparoscopy for oocyte retrieval. However, other authors have shown comparable rates of pregnancy even after the occurrence of the LH surge (3). There is little information on the influence on IVF of an elevated P before, during, and after an endogenous LH surge or the injection of human chorionic gonadotropin (hCG), although it is suggested that a rise in P or 17-OH-progesterone is closely associated with the timing of the onset of the LH surge (4,5). We believe it is important to determine when the level of P begins to rise in relationship to the LH surge and, also, the influence of P levels and timing of P elevation around the LH surge or injection of hCG on the maturation of oocytes, cleavage, and pregnancy rates in controlled ovarian hyperstimulation cycles.

MATERIALS AND METHODS

In a retrospective investigation, we analyzed hormone level in 70 cycles in 59 ovulatory women who were stimulated with clomiphene citrate (CC; Clo-mid, Shionogi & Co., Ltd.) plus human menopausal gonadotropin (hMG; Humegon, N.V. Organon). Indications for IVF were infertility of tubal origin (22 patients), unexplained (22 patients), endometriosis (9 patients), and male factor (6 patients). Patients received 100 mg CC/day from day 3 to day 7 of the menstrual cycle. A dose of 150 IU of hMG was administered by im injection every other day from day 5 or daily from day 7 or 9 to the day before either the LH surge or the hCG injection, depending upon the follicular response. Follicular growth was monitored by measuring serum estradiol (E2) and by ultrasonographic scanning of follicular diameter per vagina on days 7 and 9. Serum E2, P, and LH were measured once daily on days 3, 5, and 7 and twice daily from day 9 or 10 until the day of oocyte pickup. A surge in endogenous LH was identified by at least an 80% increase over the mean value of two of the previous day’s measurements (6). In non-surge cycles, when the dominant follicle reached 20 mm in diameter (at least two follicles were required to be present) and the E2 value exceeded 300 pg per large follicle, a dose of 5000 IU hCG was administered. Ultrasonically guided transvaginal oocyte pickup was performed 32 to 38 hr after detecting a rise in LH or 36 hr after administration of hCG. The cycle was aborted if only one follicle had developed, the rise in E2 was poor on day 7, there was an early elevation of P (that is, elevated 24 hr or more before the LH surge or the administration of hCG), or a LH surge occurred with a follicular diameter.
less than 16 mm. Details of insemination and oocyte culture have been described elsewhere (7). Specific radioimmunoassay (RIA) kits were used for assaying E2 and P (Nippon Diagnostic Products Corporation, Tokyo). The intraassay and interassay coefficients of variation (CV) of these tests did not exceed 10 and 13%. LH was measured by an enzyme immunoassay (EIA) kit (Mochida Pharmaceutical Co. Ltd., Tokyo) whose intraassay and interassay CV were below 10%. Statistical analysis of the data was performed using Student's t test or chi-square test.

RESULTS

Of the 70 treatment cycles evaluated, 19 (27%) showed a spontaneous LH surge (LH group) before the criteria for an hCG injection were fulfilled, while 31 (44%) (hCG group) did not show an LH surge. In the hCG group six male-factor cycles were excluded from further analysis. Twenty cycles were aborted.

There was no significant difference between the two groups of patients with respect to age or the number of ovarian follicles. A larger number of mature oocytes was collected from the hCG group (3.9 ± 3.0, mean ± SD) than from the LH group (2.6 ± 2.1) (Table I).

Hormonal data appear in Table II. There was no significant difference in the E2 level on Day 0, the day of the onset of LH surge or of the hCG injection. There was no difference in LH level between the LH and the hCG groups until the day of the endogenous LH surge. P levels 24 hr before the LH surge or hCG injection were 0.53 ± 0.05, respectively. P levels 12 hr before the LH surge or hCG injection (−12 hr) were 0.59 ± 0.07, respectively, not significantly different. In the LH group, the level of P at the onset of the LH surge (Day 0) was 0.91 ± 0.63, significantly higher than that in the hCG group. An elevated P level (>1.0 ng/ml; this value was above the mean ± 2 SD levels of Days −2 and −3, 0.43 ± 0.36; n = 68) was observed in a few cycles either before the LH surge (2/19; 11%) or before the administration of hCG (1/22; 4%) (Table III). The percentage of mature oocytes and the cleavage rate decreased when the time of P elevation was delayed to 24 hr after the surge in LH or the administration of hCG. Pregnancy occurred only in the cycles having a P elevation at 0 or +12 hr in both groups (Table III).

DISCUSSION

The frequency of the endogenous LH surge in patients receiving ovarian hyperstimulation for IVF is reported to range from 21.5 to 33.3% (2,8). The incidence of endogenous LH surge in our CC + hMG stimulation cycles conducted between April and December 1989 was comparable (27%). This surge occurred in the morning of 17 of 19 cycles. In