The Predictive Value of Serum Progesterone and 17-OH Progesterone Levels on *in Vitro* Fertilization Outcome*

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**Purpose:** In order to identify parameters which predict prognosis for success with *in vitro* fertilization, 17-hydroxyprogesterone and progesterone levels were evaluated in 254 patients undergoing 296 *in vitro* fertilization cycles. Selected response and outcome data were recorded.

**Results:** Patients with intermediate values of serum progesterone (0.7–0.8 ng/ml) at the time of human chorionic gonadotropin administration achieved significantly higher pregnancy rates than patients with lower (<0.7 ng/ml) or higher (>0.8 ng/ml) levels. The clinical pregnancy rates were 46%, 31%, and 27% respectively (P = 0.02). There was no change in 17-hydroxyprogesterone concentration which predicted a higher pregnancy rate.

**Conclusion:** Excellent clinical pregnancy rates were noted in cycles with a progesterone level of 0.7–0.8 ng/ml, as well as good results in cycles above 0.8 ng/ml. There is therefore no reason to administer human chorionic gonadotropin at a smaller follicle size to prevent a rise in serum progesterone.

**KEY WORDS:** *in vitro* fertilization; serum progesterone; 17-OH-progesterone.

**INTRODUCTION**

One of the essential components of a successful *in vitro* fertilization/embryo transfer (IVF-ET) cycle is the procurement of mature oocytes that will develop into embryos with good implantation potential. A variety of ovulation induction protocols have been utilized to achieve this goal. The parameters by which the quality of the developing oocytes can be measured and the markers of optimal maturity remain controversial. Ultrasonographic measurement of follicle size is an important means of assessing follicle maturity used by most programs. A variety of measurement methods are used with the optimal size of the lead follicles at human chorionic gonadotropin (hCG) trigger varying between 16 and 18 mm in most programs (1). Serum estradiol (E2) levels are useful in evaluating follicle development but their value in identifying optimal maturity is limited by the variable amount produced by small and medium sized follicles (1).

A number of studies, in cycles without pituitary down regulation, have demonstrated the adverse effect of a spontaneous luteinizing hormone (LH) surge on oocyte maturation, recovery, and fertilization rates (2,3). The elevation in serum progesterone (P4) levels associated with an LH surge has been reported to lead to a decreased success rate (4,5). The value of serum P4 levels at the time of hCG trigger as a predictor of IVF success in assisted reproduction cycles using gonadotropin-releasing hormone agonist (GnRH-a) for pituitary suppression is highly controversial. Conflicting data has been reported by a number of programs. Schoolcraft reported on 40 pregnancies resulting from 74 embryo transfers (54%) when the P4 level was <0.5 ng/ml on the day of hCG administration, 10 pregnancies resulted from 41 transfers (24%) when the level was 0.5–0.9 ng/ml, and only 2 pregnancies in a group of 18 transfers with a P4 level above 0.9 ng/ml (6). Silverberg *et al.* reported on 9 pregnancies arising from 17 transfers (53%) when

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the P₄ level was <0.4 ng/ml, 11 pregnancies resulted from 76 transfers (17%) when the P₄ level was 0.5–0.8 ng/ml, and no pregnancies resulted from the 14 transfers with a P₄ level above 0.8 ng/ml (7).

A number of other studies have found no adverse effect of an elevated P₄ level at the time of hCG trigger. Edelstein et al. reported that 9 clinical pregnancies resulted from 29 cycles (32%) with a P₄ level > 0.8 ng/ml which was not significantly different from the 21 pregnancies occurring in 72 cycles (29%) with a P₄ level of <0.9 ng/ml (8). Givens et al. reported 42 clinical pregnancies in 135 cycles (31%) with a P₄ level >0.9 ng/ml and 18 pregnancies in 54 cycles (33%) with P₄ levels <0.9 ng/ml (9).

The studies demonstrating an adverse effect of a P₄ elevation led Daly et al. to monitor serum 17-hydroxyprogesterone (17-OHP) levels in an attempt to preempt a rise in progesterone (10). They reported no adverse effect on pregnancy rates with a rise in P₄ and interestingly found that a rise of 1 ng/ml in 17-OHP level from the baseline to the level at the time of hCG administration was essential if pregnancy was to be achieved.

Our study has evaluated the importance of serum P₄ levels at the time of hCG trigger and 17-OHP level elevation from baseline to the level at the time of hCG administration as predictors of IVF success.

MATERIALS AND METHODS

A total of 254 patients undergoing 296 consecutive IVF-ET cycles performed between October 1991 and November 1994 at the Shady Grove Fertility Center in women <40 years old were examined. Analysis was limited to patients who underwent pituitary suppression with a GnRHa and subsequent ovarian stimulation with human menopausal gonadotropins (hMG) (11). All patients received subcutaneous (SC) injections of leuprolide acetate (LA; Lupron, TAP Pharmaceuticals, Chicago, IL) 1.0 mg/day beginning in the midluteal phase of the menstrual cycle. All patients had negative quantitative serum pregnancy tests prior to ovarian stimulation. Ovarian stimulation with hMG (Pergonal, Serono Laboratories, Inc., Norwell, MA) was initiated after the patient experienced withdrawal uterine bleeding, a baseline sonogram revealing no follicular cyst >10 mm in diameter, and a serum E₂ level <50 pg/ml. The daily LA dose was then decreased to 0.5 mg/day. The hMG dose was individualized based on the patients age, diagnosis, and previous stimulation history. Patients underwent serial transvaginal sonography, and serum E₂ and P₄ measurements daily after 3 days of hMG stimulation. After a baseline value was obtained, the serum 17-OHP level was measured daily during the monitoring phase in 175 cycles (155 patients) between October 1993 and November 1994. The hCG (Profasi, Serono Laboratories) was administered in a single intramuscular dose of 10,000 IU when at least two follicles measured >18 mm using a 5-MHz vaginal probe at a 40-mm focus (General Electric Medical Systems, Monterey Park, CA) as assessed by the mean of the two largest diameters. The minimum serum E₂ concentrations of >500 pg/ml. The serum P₄ and 17-OHP levels did not influence our decision to administer hCG. Transvaginal follicle aspiration was performed 34–36 h after hCG administration. Oocytes were cultured in Human Oviductal Fluid (HOF) media (Fertility Products, Inc., Rockville, MD) supplemented with 10% maternal serum. After 4–8 h, oocytes were inseminated with 50,000 motile sperm per milliliter. Embryos were transferred 46–48 h postretrieval. Luteal support was provided by daily progesterone in oil injections (50 mg intramuscularly) starting on the day after embryo transfer for all patients whose maximum E₂ exceeded 2000 pg/ml. In patients with a peak E₂ of less than 2000 pg/ml, hCG 3333 IU was given intramuscularly on days 3, 6, and 9 after retrieval. For male factor patients, high concentration microinsemination techniques were used (13). No micromanipulation techniques were utilized. A quantitative serum beta-hCG test was performed 13 days after embryo transfer in patients who received progesterone for luteal support, and 17 days after retrieval in patients who received hCG. Transvaginal sonographic documentation of fetal viability was performed in all patients with a rising beta-hCG titer. Clinical pregnancy was defined as the presence of an intrauterine gestational sac documented by transvaginal sonography. An ongoing/delivered pregnancy includes ongoing pregnancies with documented cardiac activity and pregnancies that resulted in the delivery of live infants.

We evaluated for the following parameters: age, diagnosis, baseline day 3 follicle-stimulating hormone (FSH), a number of ampules of hMG, serum P₄ levels, serum 17-OHP levels, maximum E₂ levels, number of oocytes retrieved, fertilization rates, and clinical pregnancy rates. All the serum laboratory values were assayed at DAS (Diagnostic Assay Services, Inc., Gaithersburg, MD). The FSH levels