CLINICAL ASSISTED REPRODUCTION

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.

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INTRODUCTION

In vitro fertilization–embryo transfer (IVF-ET) pregnancy rates have frequently been reported to be inversely related to serum progesterone (P_4) 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

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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°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

a 3-hr room-temperature incubation. These values were determined daily during patients' IVF-ET cycles. Interassay coefficient of variation, intraassay coefficient of variation, and sensitivity were 6.4%, 2.7%, and 5 pg/ml, respectively. Serum P_4 was measured with the same type of RIA provided by the same manufacturer, again according to manufacturer's instructions, including a 3-hr incubation at room temperature. P_4 levels on the day after hCG were determined in a single assay. The majority of P_4 levels on the day of hCG was determined in a single assay; the final 25 were determined on a daily basis after the incorporation of P_4 levels on the day of hCG into our clinical IVF-ET protocol. Interassay coefficient of variation, intraassay coefficient of variation, and sensitivity were 11.8%, 8.9%, and 0.05 ng/ml, respectively.

All statistical calculations were performed using the True Epistat (Epistat Services, Richardson, TX) statistical package on an IBM (International Business Machines, Boca Raton, FL) personal computer. Pearson's r was used to assess correlations between predictor variables. Stepwise multiple logistic regression analysis was used to determine those predictor variables correlated with cycle outcome (clinical pregnancy, ongoing/delivered pregnancy). Inclusion and exclusion criteria for the model were $P = 0.05$.

RESULTS

One of the 114 IVF-ET cycles studied, 28 resulted in clinical pregnancy. Twenty-three of the 28 clinical pregnancies culminated in a live birth, and 5 ended in spontaneous abortion. Thus, the clinical and ongoing/delivered pregnancy rates for the cycles studied were 24.6 and 20.2%, respectively. Five cycles resulting in preclinical (biochemical) pregnancy are included among the 86 unsuccessful cycles.

Clinical characteristics and oocyte, fertilization, embryo, and cryopreservation data are summarized in Table I. Patient age, etiology of infertility (expressed as percentage tubal factor), number of oocytes retrieved, number of mature, immature, atretic, and damaged oocytes, fertilization rate, number of polyspermic fertilizations, and number of embryos transferred were not different among the three groups. Intensity of ovarian stimulation, as reflected in both dosage and duration of gonadotropin treatment, was moderately less in clinical pregnancy and ongoing/delivered pregnancy cycles, but the difference was not statistically significant. Mean number of embryos cryopreserved did not differ significantly among the patient groups, but the occurrence of embryonic development sufficient to allow any cryopreservation was significantly associated with clinical pregnancy ($P < 0.05$) and ongoing/delivered pregnancy ($P < 0.01$) by multiple logistic regression analysis.

P_4 and E_2 levels on the day of and day after hCG are presented in Table II. Multiple logistic regression analysis revealed a significant inverse association between P_4 levels on the day after hCG and clinical pregnancy ($P < 0.05$). P_4 levels on the day of hCG were also inversely associated with clinical pregnancy ($P < 0.01$), as has been reported from

Table I. Clinical and Cycle Parameters Related to Cycle Outcome[a]

	Nonpregnancy ($N = 86$)	Clinical pregnancy ($N = 28$)	Ongoing/delivered pregnancy ($N = 23$)
Age (yr)	33.1 ± 0.4	32.5 ± 0.9	32.2 ± 1.0
Etiology (% tubal)	72.7	75	69.6
Days of gonadotropin R_x	9.02 ± 0.20	8.54 ± 0.25	8.70 ± 0.26
Total dose of gonadotropin R_x (IU)	2666 ± 113	2383 ± 126	2369 ± 137
Oocytes retrieved	13.5 ± 0.76	13.5 ± 1.3	14.4 ± 1.4
No. mature	11.3 ± 0.64	11.9 ± 1.2	12.7 ± 1.3
No. immature	1.2 ± 0.20	0.82 ± 0.25	0.91 ± 0.29
No. damaged	0.67 ± 0.12	0.54 ± 0.15	0.57 ± 0.18
No. atretic	0.24 ± 0.06	0.21 ± 0.09	0.22 ± 0.11
Fertilization rate (%)	80.3 ± 2.0	77.3 ± 4.5	74.7 ± 5.1
Polyspermic fertilizations	0.70 ± 0.11	0.57 ± 0.15	0.61 ± 0.17
Embryos transferred	3.80 ± 0.08	3.75 ± 0.08	3.78 ± 0.09
Embryos cryopreserved	2.4 ± 0.39	3.1 ± 0.66	3.3 ± 0.70
Cycles with cryopreservation (% of total)[b]	42 (49%)	20 (71%)	18 (78%)

[a] Where indicated values are mean ± SE.
[b] Correlated with clinical pregnancy ($P < 0.05$) and ongoing/delivered pregnancy ($P < 0.01$) by multiple logistic regression analysis.

Table II. Progesterone (P_4) Concentrations, Estradiol (E_2) Concentrations, and P_4/Oocyte Ratios Related to Cycle Outcome[a]

	Nonpregnancy ($N = 86$)	Clinical pregnancy ($N = 28$)	Ongoing/delivered pregnancy ($N = 23$)
P_4 day of hCG (ng/ml)[b]	0.67 ± 0.03	0.50 ± 0.04	0.52 ± 0.04
P_4 day after hCG (ng/ml)[c]	2.82 ± 0.16	2.25 ± 0.23	2.33 ± 0.27
E_2 day of hCG (pg/ml)	1595 ± 89	1351 ± 138	1421 ± 155
E_2 day after hCG (pg/ml)	2100 ± 106	1804 ± 180	1900 ± 204
P_4/oocyte day of hCG (ng/ml · oocyte)[d]	0.067 ± 0.009	0.046 ± 0.005	0.043 ± 0.005
P_4/oocyte day after hCG (ng/ml · oocyte)[e]	0.252 ± 0.020	0.186 ± 0.016	0.176 ± 0.016

[a] Values are mean ± SE.
[b] Correlated with clinical pregnancy ($P < 0.01$) and ongoing/delivered pregnancy ($P < 0.02$) by multiple logistic regression analysis.
[c] Correlated with clinical pregnancy ($P < 0.05$) by multiple logistic regression analysis.
[d] Correlated with clinical pregnancy ($P < 0.05$) and ongoing/delivered pregnancy ($P < 0.02$) by multiple logistic regression analysis.
[e] Correlated with clinical pregnancy ($P < 0.02$) and ongoing/delivered pregnancy ($P < 0.02$) by multiple logistic regression analysis.

our IVF-ET program previously (5). Neither E_2 on the day of hCG nor E_2 on the day after hCG correlated significantly with pregnancy.

To assess the effect of the degree of luteinization of the individual oocyte-containing follicles on cycle outcome, we analyzed the quotient resulting from division of the P_4 concentration by oocyte number for both the day of hCG and the day after hCG for each individual patient. These indices of mean individual follicular luteinization very likely are crude; the extent of luteinization probably varies among the different follicles in any individual patient. Nevertheless, this ratio gives some estimate of the extent of luteinization of the follicles in individual patients and appears to be the best way available with current clinical modalities to estimate this parameter.

The results of the mean individual follicular luteinization indices are also presented in Table II. Multiple logistic regression analysis revealed a significant association between lack of follicular luteinization (low P_4/oocyte quotient) and clinical pregnancy for both the day of hCG ($P < 0.05$) and the day after hCG ($P < 0.02$). Multiple logistic regression analysis also revealed a significant association between a low P_4/oocyte quotient and ongoing/delivered pregnancy for both days ($P < 0.02$). The concentration of P_4 was significantly associated with ongoing/delivered pregnancy only on the day of hCG ($P < 0.02$), and not on the day after hCG.

Other statistical correlations of note, as assessed by Pearson's correlation coefficient, were as follows. All four hormone levels (E_2 day of hCG, E_2 day after hCG, P_4 day of hCG, and P_4 day after hCG) correlated significantly with each of the other three hormone levels ($P < 0.01$). Number of oocytes retrieved also correlated significantly with all four hormone levels ($P < 0.01$). Total dosage of gonadotropins was significantly inversely associated both with E_2 levels ($P < 0.01$) and with P_4 on the day after hCG ($P < 0.05$), but not with P_4 on the day of hCG.

Despite the significant statistical relationships between P_4 the day of and day after hCG and oocyte number, and between P_4 the day of and day after hCG and clinical pregnancy, oocyte number and clinical pregnancy were not significantly associated by multiple logistic regression analysis, nor did a significant association exist between oocyte number and ongoing/delivered pregnancy.

DISCUSSION

In this study a significant correlation between IVF-ET success (clinical pregnancy) and low serum P_4 concentration on the day after hCG was observed. The same correlation was previously noted in our program for P_4 concentration on the day of hCG (5). Thus, it can be concluded that, in our IVF-ET program, there is at least a 2-day period in the periovulatory interval during which elevated P_4 concentration is in some way a predictor of diminished IVF-ET success. The possibility exists that the duration of time during which elevation of P_4 is associated with poor outcome extends even longer than 2 days. There are no data to suggest that an elevated P_4 2 days after hCG (day of retrieval) is deleterious, but we and others have published data suggesting that elevated P_4 in the days immediately before administration of hCG is also detrimental (3,5). Whether the P_4 elevations observed in unsuc-

cessful cycles are of a sufficient magnitude and duration to advance endometrial maturation so severely that implantation is impaired is unknown. Some support for this possibility is provided by previous studies in which a significant association between increased periovulatory P_4 concentration and advanced endometrial maturation was noted (12–15). More recent studies of the role of endometrial receptivity have focused on the relationship between endometrial pattern as assessed by transvaginal U/S and IVF-ET success. The U/S appearance of the endometrium changes cyclically in conjunction with the events of the menstrual cycle (16). The late follicular phase is characterized by a trilaminar appearance of outer and central hyperechoic "lines" separated by hypoechoic regions, the luteal phase by a homogeneously hyperechoic pattern. In studies of natural (16), stimulated (17), and hormone replacement (18) cycles, P_4 appears responsible for the transition from trilaminar to hyperechoic pattern. Eight recent studies have reported increased IVF-ET pregnancy rates in patients with trilaminar patterns around the time of hCG relative to patients with hyperechoic patterns (19–26). In one study, both endometrial pattern and P_4 concentration were determined on the day after hCG, and P_4 concentrations were increased in the hyperechoic group (22).

Because P_4 causes the transition from trilaminar to hyperechoic endometrium (16–18), and hyperechogenicity around the time of hCG administration for IVF-ET is a bad prognostic sign (19–26), elevated P_4 concentrations around the time of hCG administration theoretically could impair IVF-ET success by causing pathologic acceleration of endometrial maturation. Three other lines of evidence, however, support other hypothetical mechanisms, particularly the possibility that P_4 is a marker of diminished oocyte quality.

First, several clinical trials have been performed in which P_4 (25–100 mg intramuscularly) was administered on the day of hCG (27–31). If the relatively small endogenous increases in P_4 previously shown to be deleterious impair success via an effect on endometrium, one would expect the much greater increases in P_4 occurring with injection to reduce pregnancy rates. No such reductions have been seen; instead, no change (27–30) or even a significant increase (31) in pregnancy rates occurred.

Second, the largest and most recent studies from donor oocyte programs suggest that the window of maximum endometrial receptivity is wider than previously believed, 6 days (ET from cycle days 15 through 20) (32). The existence of such a wide window of receptivity would diminish the likelihood that small increases in P_4 could advance maturation so severely that implantation would be completely prevented. In a related line of investigation, Bergh and Navot (33) used a hypersensitive hCG assay (lowest limit of detection, 1.0 mIU/ml) to determine the exact time of implantation in ET cycles producing normal pregnancies. Implantation was critically dependent on embryonic age and independent of endometrial stage within the window of time studied (transfers performed between day 15 and day 19), again suggesting that the endometrium retains maximal receptiveness to implantation over a wide range of developmental stages.

Third, premature P_4 production presumably reflects premature activation of granulosa cell LH/hCG receptors. A number of other follicular events linked to premature LH/hCG receptor activation and also associated with reduced IVF-ET success have been reported. Those events include relatively increased follicular fluid cyclic adenosine monophosphate (cAMP) at the time of retrieval (34), relatively increased granulosa cell α-inhibin messenger ribonucleic acid (mRNA) at the time of retrieval (35), and relatively diminished serum E_2 on the day after hCG administration (4). The linkage of these different markers of premature granulosa cell LH/hCG receptor activation with poor IVF-ET outcome suggests that the premature receptor response and its attendant effects on oocyte development may be the important pathophysiologic event leading to lower pregnancy rates in elevated P_4 cycles.

Our study appears to conflict with the only other published study of P_4 concentrations on the day after hCG administration in GnRH analogue-pretreated IVF-ET cycles. That study, by Penzias *et al.* (36), reported no significant difference in P_4 concentrations between successful and unsuccessful cycles. A number of differences between the two studies (differences in patient populations, hMG dosages, criteria for hCG administration, etc.) might account for this discrepancy. One particularly important difference between the two studies is the discrepant effect of oocyte yield. In the study by Penzias *et al.*, successful cycles were associated with a significantly increased oocyte yield and no significant difference in P_4 concentration. In this study, successful cycles were characterized by no difference in oocyte yield and a significantly lower

P_4 concentration. The apparent discrepancy between the two studies may be resolved by the observation that in both studies the P_4 concentrations per oocyte recovered were lower in successful cycles. This parameter, P_4 per oocyte, is the index of mean individual follicular luteinization we analyzed and found to be significantly correlated with clinical ($P < 0.05$) and ongoing/delivered ($P < 0.02$) pregnancy in our study. Thus, on the basis of just these two studies, it appears that diminished premature follicular luteinization as reflected in a low P_4/oocyte ratio is a stronger correlate of IVF-ET success than are simple P_4 concentrations.

In summary, in this study we have demonstrated a significant association between elevated P_4 on the day after hCG administration and IVF-ET failure. These results extend the window of time in the periovulatory period during which P_4 elevation is associated with poor outcome to at least 2 days, and perhaps more. The pathophysiologic mechanism which explains the link between elevation of P_4 and diminished IVF-ET success remains uncertain. Substantial arguments can be made for two hypotheses: (i) an effect on endometrial receptivity and (ii) a marker of impaired follicle/oocyte quality, possibly due to premature or dyssynchronous LH/hCG receptor activation. The latter appears to be supported by a particularly diverse group of findings in previous studies and by the strong associations between IVF-ET success and both P_4/oocyte ratios and progression to cryopreservation found in this study. Hopefully, further studies with both existing and as-yet-undeveloped techniques will further clarify the critical determinants of IVF-ET success and, thereby, point the way toward their more successful therapeutic manipulation.

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