

## SHORT COMMUNICATION

CAMDEN, NEW JERSEY

### Comparison of Luteal-Phase Support with High- and Low-Dose Progesterone Therapy on Pregnancy Rates in an In Vitro Fertilization Program

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#### INTRODUCTION

Many in vitro fertilization (IVF) programs supplement the luteal phase of the IVF cycle with extra progesterone (P) administered orally, vaginally, or intramuscularly (IM). However, Daya, in compiling statistics from all relevant studies published between 1978 and 1987, was unable to find significantly increased pregnancy rates in P-supplemented IVF cycles (1). In a similar investigation, Van Steirteghem *et al.* found no beneficial effects of 50 mg IM daily progesterone support (2), nor were there any beneficial effects of P and estradiol versus human chorionic gonadotropins (hCG).

Yet there have also been some positive reports demonstrating the benefit of P supplementation. Ben-Nun *et al.* recently published data showing a significantly higher pregnancy rate for patients undergoing IVF who were treated with supplemental P in the luteal phase, as compared to untreated controls (3). In fact, a 41.2% pregnancy rate was reported in the treated women, vs 23.3% in the untreated controls. The amount of progesterone pre-

scribed (100 mg IM daily) was significantly higher than the amount used in most fertility programs. The objective was to advance the endometrium so that at the time of transfer, it would be more similar to the endometrium at the time of implantation in natural cycles.

We report herein the results of a randomized study comparing pregnancy rates with high-dose P support (100 IM daily) to rates with low-dose luteal-phase supplementation (25 mg IM).

#### MATERIALS AND METHODS

Since the objective was to evaluate the relative effects of high- vs low-dose progesterone therapy in 100 in vitro fertilization-embryo transfer (IVF-ET) cycles, the study was to be terminated when each of the 50 females had undergone one cycle of each treatment regimen, unless a successful pregnancy occurred. The initial progesterone therapy was randomized; patients were randomly assigned to either the high (100 mg) or the low (25 mg) dose treatment group, such that 50 patients received the low dose and 50 received the higher dose in the first cycle. According to social security number, those ending with odd numbers received 25 mg P and those ending with even numbers received 100 mg P. Failure to achieve a nonaborted pregnancy would change the therapy to the alternate treatment in the next cycle. A third cycle was to be included if not all 50 females completed two cycles.

In each cycle the hyperstimulation regimen consisted of a long regimen of gonadotropin-releasing hormone (GnRH) with leuprolide acetate (LA), 1 mg subcutaneously, started on day 21 of the cycle and continued for at least 10 days (4). If both the serum P and the estradiol (E<sub>2</sub>) levels were adequately suppressed (<2 ng/ml and <40 pg/ml, respectively), the LA was to be reduced to 0.5 mg

subcutaneously daily and human menopausal gonadotropin (hMG) would be initiated at 300 IU for the first 4 days, decreased to 225 IU for 1 day, and then further decreased to 150 IU. The dosage was to be individualized until at least two lead follicles measured 17 mm in average diameter and the serum estradiol reached at least 800 pg/ml. Human chorionic gonadotropin (hCG) would then be given at a dosage of 10,000 units approximately 10 hr after the deciding serum E<sub>2</sub> was obtained. Ovum retrieval ensued 34–36 hr later, followed by embryo transfer 2 days after retrieval.

Low-dose progesterone (group 1) was initiated at 25 mg IM beginning on the day of retrieval and continued throughout the luteal phase until 16 days from hCG injection, when it would be stopped for a negative hCG beta-subunit level or discontinued if spontaneous menses occurred. The high-dose P (group 2) was started at the time of hCG injection and was similarly continued throughout the luteal phase. If pregnancy ensued, progesterone was to be continued at the same dosage throughout the first trimester.

Rates of pregnancy and spontaneous abortion were calculated for both groups and the data were statistically evaluated by chi-square analysis. The mean serum E<sub>2</sub> and P levels at the time of hCG were calculated separately for those conceiving versus those not conceiving, separated also as to the dosage of P used for luteal-phase supplementation.

## RESULTS

The data failed to demonstrate a higher pregnancy rate in group 2 patients treated with the higher dose P (8.8%) compared to the lower dose (20.3%), as seen in Table I. In fact, the trend was in the opposite direction, although not statistically sig-

**Table I.** Comparison of High- vs Low-Dose Progesterone Support of the Luteal Phase in Achieving IVF-Related Pregnancies and Preventing Spontaneous Abortion

	25 mg progesterone	100 mg progesterone
No. of cycles	59	68
No. of pregnancies	12 (20.3%)	6 (8.8%)
Outcome of pregnancies		
Ongoing second trimester	7	3
Delivered	1	1
No. of abortions	4 (33.3%)	2 (33.3%)

nificant ( $P = 0.06$ ). All pregnancies either have successfully completed the first trimester or have spontaneously aborted. There were no differences in the abortion rates in groups 1 and 2.

The mean serum E<sub>2</sub> and P levels at the time of hCG were very similar in the group that subsequently received 25 mg P support in the luteal phase whether they conceived or not (mean E<sub>2</sub>, 1359 pg/ml in conceivers vs 1080 pg/ml in nonconceivers; mean P, 0.7 ng/ml in conceivers vs 0.86 ng/ml in nonconceivers). Similarly the same trend was found in those patients given the higher, 100-mg dosage (mean serum E<sub>2</sub>, 1065 pg/ml in conceivers vs 1104 pg/ml in nonconceivers; P, 0.98 ng/ml in conceivers vs 0.86 ng/ml in nonconceivers).

## DISCUSSION

In contrast to the study by Ben-Nun *et al.* (3), not only were we unable to corroborate that the use of a higher dose of progesterone in the luteal phase (and using it earlier) leads to a higher pregnancy rate, but we, in fact, found that the opposite trend occurred. When we began this investigation, Ben-Nun and co-workers' data had not yet been published. Thus we both independently formulated the same hypothesis that advancing the endometrium might enhance the pregnancy rate. However, since this study was not initiated to corroborate or refute Ben-Nun's study, certain differences in the methodology exist which may account for the differences in our findings. These include that (a) we continued the P therapy throughout the luteal phase instead of for only 6 days and (b) Ben-Nun *et al.* divided the 100 mg P into two doses and we used only one dose.

Another important difference exists between the two studies; our design was truly randomized and prospective, whereas they compared data performed at two different time periods, i.e., during one interval all patients received high-dose progesterone and during the other time interval they received none. We realize that all programs go through periods of higher and lower pregnancy rates purely by chance.

Furthermore, the controlled ovarian hyperstimulation regimens were different. Perhaps high-dose progesterone works better with some methods of follicle stimulation than with others. We recognize that the Ben-Nun *et al.* program has had a higher

success rate than ours; their least successful group had a higher pregnancy rate (23.3%) than our best group (20.3%). Should we decide to continue this comparative study, we will attempt to follow more precisely their protocol to see if our findings are comparable.

Neither dosage in our study proved more efficacious in preventing spontaneous abortion. Since the mean serum  $E_2$  in Ben-Nun and co-workers' study at the time of hCG was about 2700 pg/ml, compared to 1104 and 1065 pg/ml, respectively, in our non-conception and conception groups receiving 100 mg P supplementation, the possibility exists that very high P support may be beneficial at very high  $E_2$  levels and detrimental at low levels. There was a total of 12 patients with  $E_2$  levels over 2000 pg/ml in our study. The pregnancy rates in this subset with 100 vs 25 mg P were zero of six (0%) and two of six, respectively (33%) (Fisher's exact test;  $P = 0.22$ ). There were two patients with levels over 2700 pg/ml in the high-dose P group and three patients over this level in the low-P group; both patients in the former group failed to conceive and two of three in the latter group conceived.

We must note that our study was not originally designed to evaluate the need for supplemental P in IVF cycles but only to compare the benefits of high- and low-dose P. A study by Smith *et al.* using a long buserelin and hMG protocol for controlled ovarian hyperstimulation (COH) concluded that luteal-phase support with hCG improved pregnancy rates (4).

Our data demonstrate that with a long leuprolide acetate/hMG regimen for COH, there does not appear to be any advantage, and perhaps is a disadvantage, to supplementing with high-dose P in the luteal phase, at least when there are only moderate elevations of the serum  $E_2$  at the time of hCG; the low-dose P therapy may have improved our rates. Further randomized prospective studies are needed to compare the efficacy of luteal-phase support with

hCG vs P, and to evaluate the ideal dosage of P support in accordance with the serum  $E_2$  levels at the time of hCG injections.

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