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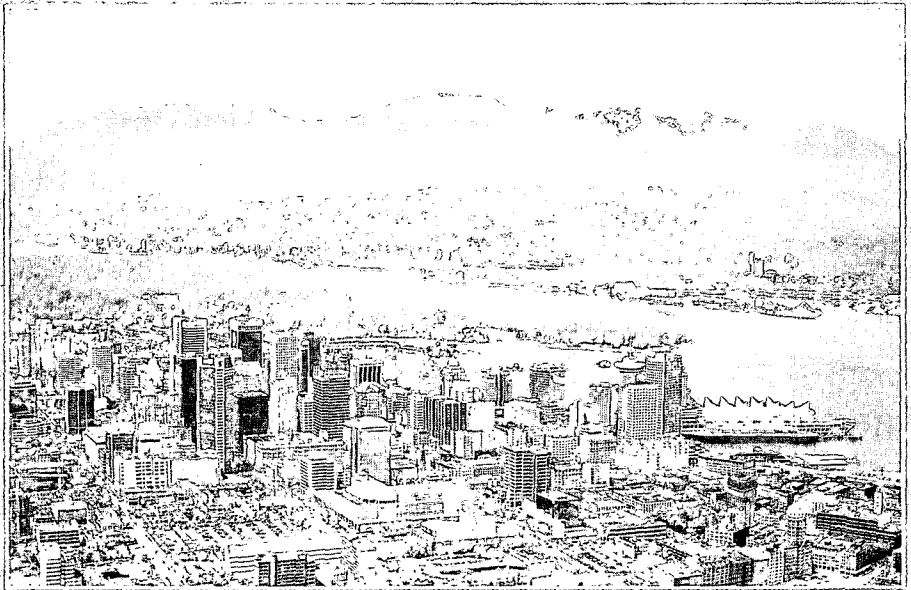
# IN VITRO FERTILIZATION AND ASSISTED REPRODUCTION

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Higher pregnancy rates  
(PRs) following in vitro  
fertilization-embryo  
transfer (IVF-ET)  
with luteal phase  
leuprolide acetate  
(LA)/gonadotropin  
hyperstimulation regimen  
if serum estradiol ( $E_2$ )  
increases by at least  
10% the day after  
human chorionic  
gonadotropin (hCG)

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SUMMARY

The objective of this study was to determine if the change in serum estradiol ( $E_2$ ) the day following human chorionic gonadotropin (hCG) in in vitro

fertilization (IVF) cycles using the luteal phase leuprolide acetate (LA)/human menopausal gonadotropin (hMG) ovarian hyperstimulation protocol was associated with pregnancy rates (PRs). The clinical PR increased as the change in  $E_2$  increased: 0% PR if  $E_2$  decreased by more than 10%; 12.2% PR if  $E_2$  remained within 10% of the level on day of hCG; and 23.8% PR if  $E_2$  increased by more than 10%. Based on these results, the clinician should consider deferring embryo transfer if the  $E_2$  levels decreased.

## INTRODUCTION

Previous studies have shown that a decrease in the serum estradiol ( $E_2$ ) level following human chorionic gonadotropin (hCG) administration in patients undergoing gonadotropin stimulated in vitro fertilization-embryo transfer (IVF-ET) cycles were associated with lower pregnancy rates (PRs) (Laufer et al, 1986; Fleming et al, 1986). The decrease in serum  $E_2$  levels following controlled ovarian hyperstimulation (COH) and subsequent reduced PRs has been attributed to premature luteinization (Salat-Baroux, 1988).

The use of gonadotropin releasing hormone agonists (GnRHa), e.g., leuprolide acetate (LA), in conjunction with gonadotropin therapy has been found to markedly reduce the frequency of premature luteinization associated with COH (Garcia et al, 1990). The study presented herein evaluated the change in serum  $E_2$  on the day after hCG when a GnRHa was used with gonadotropins for COH for IVF and its relationship to PRs.

## MATERIALS AND METHODS

A total of 269 patients who presented for infertility in a university associated out-patient facility underwent IVF-ET cycles with luteal phase LA/human menopausal gonadotropin (hMG) COH. The LA was started 1 week after ovulation and was given SC at 1 mg/day until serum  $E_2$  was <50 pg/mL and serum progesterone (P) <1 ng/mL; then hMG was started at 300 IU IM daily (the LA dosage was reduced to 0.5 mg once hMG was started). Human chorionic gonadotropin (10,000 U IM) was administered when 2 lead follicles reached an average diameter of 20 mm and the serum  $E_2$  was greater than 800 pg/mL. Sera  $E_2$ , P and luteinizing hormone (LH) were measured on the day of hCG injection and day after hCG.

Patients were divided into three groups according to the change in  $E_2$  levels from day of hCG to the day after hCG injection: decreased by more than 10% (group 1), stayed within 10% (group 2), or increased by more than 10% (group 3). Clinical PR were defined by sonographic evidence of gestational sac in the uterus.

Chi-square analysis was used to compare PRs by change in  $E_2$  levels. Analysis of variance was used to compare the mean sera levels of P and LH between groups. A p value of .05 was used.

## RESULTS AND CONCLUSIONS

Sera  $E_2$  levels the day after hCG injection increased by more than 10% in 191 cycles (71.0%) remained within 10% of the levels on the day of hCG in 67 cases (25%), and decreased by 10% or more in 11 (4%) patients. The age of patients, ovarian response (as measured by number of oocytes

Table 1 Comparison Of Sera Levels By Change In E<sub>2</sub> Following hCG (Data Presented As Mean ± Standard Deviation)

	Decrease >10% (n=11)	Within 10% of day of hCG (n=67)	Increase >10% (n=191)
Age*	34.9±4.0	33.3±3.9	33.5±3.7
Oocytes retrieved*	14.7±7.2	15.2±9.5	17.8±9.6
Fertilization rate*	51.8±18.2	56.5±24.8	54.5±25.4
# embryos transferred*	3.9±1.4	3.7±.9	3.4±1.0
Sera levels day of hCG			
E <sub>2</sub> (pg/mL)	2516.4±1791.7	2925.9±1803.8	2894.9±1492.9
P* (ng/mL)	.7±.4	1.0±.4	.8±.5
LH* (mIU/mL)	4.7±3.8	4.6±5.1	3.8±2.7
Sera levels day after hCG			
E <sub>2</sub> (pg/mL)	1632.3±1136.1	2997.0±1822.4	4090.9±2122.1
P* (ng/mL)	5.4±2.1	6.2±3.9	6.4±8.2
LH* (mIU/mL)	12.4±18.1	4.1±7.7	6.2±12.5

\* p=NS comparing means by E<sub>2</sub> groups

retrieved, fertilization rates and number of embryos transferred) and serum levels of LH and P were similar in all three groups (tab. 1).

The number of embryo transfers in each group were 8, 49, and 126, respectively. The difference in the number of oocyte retrievals and ET cycles was mainly due to the center's policy of cryopreserving all embryos and deferring ET if the patient was found to have inadequate endometrial development (i.e., thickness <10mm or a homogeneous hyperechogenic echo pattern) or the patient was considered at risk for ovarian hyperstimulation syndrome.

The clinical PRs per transfer were 0% in group 1, 12.2% in group 2 and 23.8% in group 3. The delivery rates per transfer were 0%, 10.2%, and 19.8%, respectively. The failure to attain statistical significance when comparing the PRs in the three groups can be attributed to the small sample size in the groups with decreased E<sub>2</sub> levels. To be able to detect a 15% decrease in PR with 80% power at the .05 level of significance, a sample size of 88 patients per group would be required. Therefore, for further analysis, the groups that failed to achieve at least a 10% increase in E<sub>2</sub> levels on the day after hCG (groups 1 and 2) were combined and their PR was compared to that of the group whose E<sub>2</sub> increased by more than 10%. There was a significant difference between the PR of 10.5% attained by the group that fail to attain an increase in E<sub>2</sub> of at least 10% versus the PR of 23.5% in those that did (p<.05, chi-square). The corresponding delivery rate were 8.8% and 19.8%, respectively (p=.061, chi-square).

Fourteen patients from group 1 and 2, and 44 patients in group 3 who cryopreserved all their embryos and deferred ET subsequently underwent a frozen ET. As a result of these transfers, there were 2 (14.3%) clinical pregnancies in groups 1 and 2, and 9 (20.4%) clinical pregnancies in group 3

( $p = \text{NS}$ , chi-square). The corresponding delivery rates were 14.3% and 15.9%.

The percentage of patients with a decrease in serum  $E_2$  by more than 10% from day of hCG to day after hCG was much smaller when using the luteal phase GnRHa, hMG protocol compared to previous reports where no GnRHa was used (Laufer et al, 1986; Fleming et al, 1986; Salat-Baroux, 1988). Such results could be attributed to successful prevention of premature luteinization by GnRHa treatment. Indeed, although previous reports suggested an incidence of premature luteinization up to 51% in cycles with ovarian stimulation (Garcia et al, 1990), the examined sera LH and P levels 1 day post-hCG injection in the study presented herein did not differ between patients with decreased  $E_2$  compared to the rest of the patients.

Since the number of embryos transferred were similar in all groups, the difference in PRs could either be attributed to better embryo quality in those with better  $E_2$  responses or some improvement in the endometrium allowing for better implantation. By evaluating subsequent PRs following frozen ET, the data suggest that the greater PRs with the best  $E_2$  responses after hCG is probably related to improvement in endometrium.

If more extensive data continue to confirm the poor prognosis for patients whose serum  $E_2$  levels fail to increase by at least 10% on the day after hCG, the clinician should consider cancelling the transfer, cryopreserving the embryos, and transferring them in a cycle in which there is a better endometrial environment.

#### REFERENCES

1. Fleming R, Coutts JR. Induction of multiple follicular growth in normally menstruating women with endogenous gonadotropin suppression. *Fertil Steril* 45(2):226-30;1986.
2. Garcia JE, Padilla SL, Bayati J, Baramki TA. Follicular phase gonadotropin-releasing hormone agonist and human gonadotropins: a better alternative for ovulation induction in in vitro fertilization. *Fertil Steril* 53(2):302-5;1990.
3. Laufer N, DeCherney AH, Tarlatzis BC, Naftolin F. The association between preovulatory serum 17 beta-estradiol pattern and conception in human menopausal gonadotropin-human chorionic gonadotropin stimulation. *Fertil Steril* 46(1):73-6;1986.
4. Salat-Baroux J. Prognostic value of pre-ovulatory serum progesterone, LH and oestradiol-17 beta levels in stimulated cycles for in-vitro fertilization. *Hum Reprod* 3(3):281-4;1988.

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