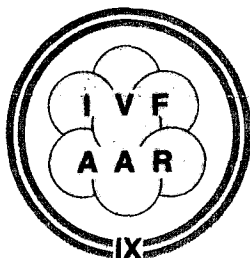


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# Subtle rise in progesterone (P) at time of human chorionic gonadotropin (hCG) may have more of an adverse effect on the endometrium than the oocyte as determined by a shared oocyte program (1)

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## SUMMARY

Previous data suggested a subtle increase in serum progesterone (P) at the time of human chorionic gonadotropin (hCG) injection without luteinizing hormone (LH) surge reduces the pregnancy rates (PRs) of women having oocyte retrievals for in vitro fertilization (IVF); this study compared PRs of recipients in a shared oocyte program according to the donors' pre-hCG P level. There was no difference in viable PRs between recipients and donors when  $P \leq 1\text{ng/mL}$ . The PR was similar for recipients when donors P was  $> 1\text{ng/mL}$  (12.7%). Donors with  $P > 1\text{ng/mL}$  had the lowest PR, 7.2%. The data suggests that the adverse effect of higher serum P without LH surge may be on the endometrium rather than the oocyte.

## INTRODUCTION

A subtle rise in serum P prior to receiving an injection of hCG has been associated with a decreased PR following IVF-embryo transfer (ET) both in cycles where no gonadotropin releasing hormone (GnRH) agonists were used to first suppress gonadotropins (2) and even in cycles using leuprolide acetate (LA) prior to human menopausal gonadotropin (hMG) to prevent premature luteinization (3,4). The rise in serum P, even without a rise in serum LH, may be secondary to induction of excess LH receptors in granulosa cells (GC) by high serum estradiol ( $E_2$ ) and follicle stimulating hormone (FSH) levels, thus making the GCs more sensitive to LH.

There is controversy as to whether this subtle rise has a detrimental effect on the oocyte or the endometrium. Mio et al. (2) evaluating CC-hMG cycles found a decrease in mature (stage 1) follicles with increasing serum P level, whereas, Silverberg et al. did not find a decrease in mature oocytes with higher sera P levels (4). Furthermore, Silverberg et al. reported two ongoing pregnancies following frozen-ET from women with increased P levels, suggesting that the adverse effect of P may not be exclusively related to damage to the oocyte (4).

The Cooper Institute for In Vitro Fertilization has a large shared donor oocyte program in which recipients in ovarian failure may share oocytes with a donor who needs IVF-ET (5). The study presented herein attempted to answer the question as to whether the adverse effect of subtle increased serum P is related to damage to oocyte or endometrium by comparing PRs from donors whose sera P levels were  $>1\text{ng/mL}$  (conversion factor to SI units 3.180) to those recipients acquiring oocytes from donors with a sera P  $\leq 1\text{ng/mL}$ . Furthermore, the study would attempt to determine if we could corroborate previous data demonstrating the association of low PRs with sera P  $> 1\text{ng/mL}$ .

## MATERIALS AND METHODS

All women undergoing IVF-ET who shared oocytes between November 1, 1991 and August 19, 1992 were evaluated. These dates were chosen because at this time the serum P assay was the same as the one used when a higher PR was found to be associated with low levels of sera P measured by the Amerlex-M RIA (Amersham Inc., Arlington Heights, IL).

The donors used the same controlled ovarian hyperstimulation (COH) regimen, i.e., a luteal phase LA-hMG regimen. Human menopausal gonadotropin (300 IU/d) was started on the 11th day of LA for four days and then reduced to 225 IU. Further changes were made in accordance with the results of serum  $E_2$  levels and number and size of follicles obtained by pelvic sonography using a vaginal transducer. Human chorionic gonadotropin was given when at least two lead follicles attained an average diameter of 18 mm and serum  $E_2$  was at least 300 pg/mL (conversion factor to SI units 3.671) per follicle.

The clinical PRs (defined as evidence of pregnancy demonstrated on ultrasound) and the viable PR (defined by a viable fetus at delivery) for each patient were then determined. The PRs were calculated according to the serum P level, i.e., either P  $\leq 1\text{ng/mL}$  or P  $> 1\text{ng/mL}$  and also

compared according to whether the patient was a donor (D) or recipient (R).

Statistical analysis comparing PRs was determined by chi-square analysis with  $p=.05$  as the level of significance.

## RESULTS AND CONCLUSIONS

The clinical PRs in donors and recipients according to serum P level at time of hCG is seen in Table 1. For this series the clinical PR for recipients was 17.4% (23/132) compared to 19/138 (13.7%) for donors. There were two spontaneous abortions in recipients with low P (2/12) and 3/11 in the other recipient group; 1/11 in the donor group with low P and 3/8 in donors with high serum P. The viable PRs are also seen in Table 1. Chi-square analysis failed to reveal any significant difference between groups with this sample size. Based on previous differences in PRs in patients undergoing IVF-ET and serum P  $\leq 1\text{ng/mL}$  at the time of hCG (29/67, 43.2%) vs those with a serum P of 1.1 to 2.0ng/mL (6/38, 15.8%) we estimated that a sample size of 125 would be sufficient (Check JH, Choe J, Nowroozi K, Hoover L, abstract). Unfortunately, the PRs for patients with sera P levels  $< 1\text{ng/mL}$  at time of hCG were not as high as previously found. Power analysis indicated that to detect a difference of 7% in the live PR for donors with various levels of serum P with 80% power at the .05 significance level, 328 cases per group would be required.

**Table 1** Clinical and viable IVF pregnancy rates in donor and recipients according to serum progesterone level at time of human chorionic gonadotropin injection

|                            | P $\leq 1.0\text{ng/mL}$ |           | P $> 1.0\text{ng/mL}$ |           |
|----------------------------|--------------------------|-----------|-----------------------|-----------|
|                            | Donor                    | Recipient | Donor                 | Recipient |
| Total number               | 69                       | 69        | 69                    | 63        |
| Number pregnant (clinical) | 11                       | 12        | 8                     | 11        |
| % pregnant clinical        | 15.9                     | 17.3      | 11.6                  | 17.5      |
| Number SAB*                | 1                        | 2         | 3                     | 3         |
| Number pregnant viable     | 10                       | 10        | 5                     | 8         |
| % pregnant viable          | 14.4                     | 14.4      | 7.2                   | 12.7      |

\* SAB - spontaneous abortion

A recent study by Fanchin et al. corroborated a decreased PR associated with slight premature rise of P at time of hCG (6). These

authors presented data demonstrating that even these slight elevated levels of P were sufficient to advance secretory transformations of the endometrium (6).

Schoolcraft et al. demonstrated that pre-hCG elevation in serum P did not result in lower oocyte fertilization and cleavage rates but yet lowered the PR (3). The fact that in two other studies (4,6) there was an equal number of embryos available for transfer in both the high and the low P groups suggests that the adverse effect of elevated P is not on oocyte quality or embryo development.

Fanchin et al. hypothesized that "pre-hCG increases in plasma P that sporadically occur in IVF-ET cycles might alter IVF-ET outcome primarily by affecting endometrium receptivity to embryo implantation. It is, indeed, conceivable that a pre-hCG elevation in plasma P could advance the secretory transformation of the endometrium, thereby leading to a premature closure of the window of receptivity before embryos are available for transfer".

Fanchin et al. (6) suggested that, ultimately, the study of outcome of transfers of cryopreserved embryos originating from IVF-ET cycles where P at time of hCG was either high or low could test the hypothesis that the adverse effect of elevated P is on endometrium rather than embryo quality. However, another method of testing this hypothesis is by studying the outcome of embryo transfers according to the level of serum P in the oocyte donors in a shared oocyte program, as in the study presented herein.

Unfortunately, these preliminary data did not demonstrate as high a PR in patients with sera P  $\leq$  1ng/mL as before, so that the higher viable PR in the donors (14.4%) from the low P group vs the high P group (7.2%), without demonstrating any difference in viable PRs of recipients from these respective groups (14.4 vs 12.7%), should only be considered supportive, but not conclusive evidence that the adverse effect of serum P is on the endometrium. If the same PR and differences and numbers of shared donor-recipient cycles are maintained we estimate it will take another two years to gain sufficient data to attain significance.

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