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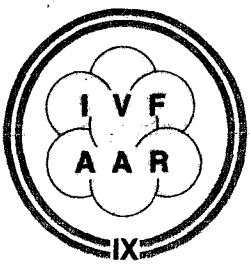

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A 36 hour time of retrieval from human chorionic gonadotropin (hCG) injection may produce better pregnancy rates (PR) than a 34 hour interval

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SUMMARY

The purpose of this study was to determine the best interval for retrieval of oocytes following human chorionic gonadotropin (hCG) using a down-regulated gonadotropin protocol for in vitro fertilization-embryo transfer (IVF-ET) as measured by increased fertilization and pregnancy rates (PRs). A retrospective study of 385 IVF-ET cycles was conducted in which cycles were classified by the number of hours between hCG and retrieval as follows: 34, 35, 36, 37 or more. There was no difference in the fertilization rates in the four time intervals; however, the PRs for the interval 37 hours or more was higher than the other groups (31.0%, 14.2%, 10.1%, 20.9%, chi-square, $p<.05$). The PR for the 36 hours group was 21.1% v 12.9% for the 38 hours group ($p>.05$, chi-square) in a subsequent prospective study.

INTRODUCTION

Previous data from Thorten et al. evaluating whether increasing the retrieval interval from time of human chorionic gonadotropin (hCG) from 34 to 37 hours (hrs) in patients undergoing in vitro fertilization (IVF) did not demonstrate any effect on the number or quality of oocytes retrieved or on the ultimate pregnancy rate (PR); however, Thornton's study

evaluated IVF cycles using clomiphene citrate (CC)-human menopausal gonadotropin (hMG) as the controlled ovarian hyperstimulation (COH) regimen and did not use gonadotropin suppression with a gonadotropin releasing hormone agonist (GnRHa) (1).

Many IVF centers now use GnRH agonists to prevent luteinization prior to stimulation with gonadotropin in their COH protocols for IVF-ET (2,3). Since luteinizing hormone (LH) is suppressed when GnRH agonists are used, compared to a COH regimen where they are not used, the question arises as to whether the oocytes might not be fully matured when retrieved at a shorter interval of 34 hrs; the retrieval of somewhat immature oocytes may lead to reduced fertilization and or reduced PRs.

The study presented herein evaluated, first retrospectively and second prospectively, the effect of the interval from hCG injection to retrieval time on subsequent fertilization and PRs.

MATERIALS AND METHODS

Retrospective study

The study included all IVF-ET cycles for the year 1991, in which a GnRHa was used starting in the mid-luteal phase and continuing for at least ten days before hMG 300 U/day was given. The GnRHa used was leuprolide acetate (LA); our modification has been previously described (4,5). The luteal phase LA-hMG COH regimen was used in all couples registering for IVF unless they were potential or known poor responders.

The retrievals had been planned for 34 hrs following hCG. The time of retrieval was logged, but because of various delays, patients frequently had retrievals more than 34 hrs after the administration of hCG. Cycles were classified into four groups based on the time interval between hCG and oocyte retrieval: group 1 - all cycles in which the time interval was at least 34 hours but before 35 hours; group 2 - all cycles in which the time interval was at least 35 hours but before 36 hours; group 3 - all cycles at least 36 hours but before 37 hours; group 4 - all cycles where the interval was 37 hours or more.

The mean age, number of oocytes retrieved, fertilization rate, and number of embryos transferred for the cycles in each time interval were compared using analysis of variance at the .05 level of significance. The viable PRs from each time interval were compared using chi-square analysis at the .05 level of significance. The results then helped us to decide that a prospective study was warranted; furthermore, the retrospective data helped us to choose the two time intervals to evaluate for the prospective study.

Prospective study

Patients undergoing an IVF cycle using the luteal phase LA-hMG COH regimen for a six month period in 1992 were eligible for this study. Patients were randomized into two treatment groups using the following methodology: those taking hCG on Friday, Saturday, Sunday or Monday had their retrieval 36 hrs later, whereas, those taking hCG on Tuesday, Wednesday, or Thursday would have retrievals 38 hrs from hCG. Simultaneous retrievals by two physicians were occasionally performed to prevent delays in the retrievals. The mean age, number of oocytes retrieved, fertilization rate and number of embryos transferred were compared between the two groups using a two-tailed t-test for independent

groups at the .05 level of significance. The viable PRs were compared using chi-square analysis at the .05 level of significance.

RESULTS AND CONCLUSIONS

Retrospective study:

Three hundred eighty five IVF-ET cycles were included in this study. When classified by time interval between hCG injection and oocyte retrieval, there were 190 cycles in group 1, 119 cycles in group 2, 43 cycles in group 3 and 29 cycles in group 4. The mean age of the women (range 32.9 to 34.8 years) in each group did not differ.

The time interval between hCG and the retrieval had no effect on the mean number of oocytes retrieved, fertilization rate, or number of embryos transferred. However, there was a difference in the viable PRs observed in the four groups: 14.2% (27/190) for group 1, 10.1% (12/199) for group 2, 20.9% (9/43) for group 3 and 31.0% (9/29) for group 4 (chi-square, $p<.05$). To further examine this difference, the chi-square was partitioned to compare the PR of group 1 vs group 2 ($p>.05$); group 1 and 2 vs group 3 ($p>.05$); group 1, 2 and 3 vs group 4 ($p<.05$). Thus, the retrospective study showed that there was a higher PR when the time interval was 37 hours or more. Since the number of cycles in groups 3 and 4 were much smaller than group 1 and 2, a prospective study was planned to compare the rates at the longer time intervals to see if the higher PR was reproducible.

Prospective study

Sixty nine cycles were included in this study, 38 in group 1 and 36 in group 2. The mean age of the patients in the two groups were the same (t-test, $p>.05$). The mean number of oocytes retrieved, fertilization rate and number of embryos transferred were also the same in both groups (t-test, $p>.05$). The viable PRs were 21.1% (8/38) for the 36 hour group and 12.9% (4/31) for the 38 hour group (chi-square, $p>.05$).

Using conventional gonadotropin therapy or CC-gonadotropin, premature surge of LH may lead to cancellation of 15-30% of cycles (6). Therefore, a 34 hr interval from hCG to retrieval was considered appropriate. Part of this decision was based on choosing an interval where oocyte maturation can be achieved, but yet reducing the risk of cancellation for premature luteinization.

The use of GnRH agonists has allowed for only rare cancellations for premature luteinization in COH regimen for IVF-ET (5). The question then arose as to whether a better PR might be achieved by delaying retrieval a few hrs to allow for better oocyte maturation and a greater chance for completion of the first meiotic process.

Initially, a prospective study comparing the 34 hr interval from hCG to retrieval (our previous standard) to a 36 hr interval, was planned. However, after evaluating the retrospective data, a prospective study comparing a 36-38 hr interval seemed the most appropriate time period to examine because even though not significant, the PRs with an interval of <36 was 12.6%, >36 - <37 was 20.9%, and with ≥ 37 was 31.0%.

Though no statistical differences were found in the prospective study, the data shows no advantage in waiting for the longer interval for retrieval when using a GnRHa- gonadotropin COH regimen. A prospective study comparing a 34 to 36 hr interval is still needed to

scientifically state that the latter is more likely to result in pregnancies. Nevertheless, since the incidence of premature luteinization is very low and the retrospective data did suggest a lower PR with only a 34 hr interval when a GnRH-a is used, we have changed to a 36 hr time interval.

Prospective studies comparing 34-36 hour intervals with other COH regimens, e.g., the flare technique (7), or clomiphene-gonadotropin, gonadotropins only, or ultra-short GnRHa-gonadotropin (8) regimen might be considered in the future.

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