THE COMPARISON OF TWO DIFFERENT LUTEAL PHASE SUPPORT IN IVF PATIENTS

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ABSTRACT

Objective: The purpose of this retrospective study was to compare 2 different methods of luteal phase support in in vitro fertilization patients after embryo transfer.

Methods: In 101 embryo transferred cycles 35 of the patients were given hCG supplemental (starting the day before embryo transfer 1500 IU every 3 days for 6 times), 54 of them were given progesterone in oil (50 mg/day, IM injection, 20 days) randomly, except when E2 levels exceeded 3000 pg/ml. We had 9 pregnancies in hCG group, 10 with progesterone group.

Results: The comparison of results showed no significant difference between the 2 groups. Of the 9 patients who used hCG 6 aborted, of the 10 pregnant patients in progesterone group, 4 aborted.

Conclusion: There was no difference from pregnancy rate point of view, but hCG group had a trend to abort more frequently (Fischer's exact test, p=0.06).

Key Words: In-vitro fertilization, luteal phase, ovulation induction, progesterone.

INTRODUCTION

There appears to be a reasonable rationale for luteal support in infertility treatment involving ovarian stimulation particulary when this is combined with assisted reproduction, as these cycles may often display markedly shortened luteal phases. However, published reports of randomized control trials, assessing luteal phase treatments using progesterone (P) or hCG support, fail to show significant improvement in pregnancy rates, although there usually seems to be a trend implying a benefit (1,2).

Establishment of a successful pregnancy reguires three major stages, namely fertilization, implantation and postimplantation embryo development. The efficiency of fertilization, both in vivo and in vitro is about 85%, however fecundability is only 20-25% for women <30 years of age (3). Major limiting step in the reproductive process is the implantation stage which requires complex preparation of the endometrium beginning in the proliferative phase and extending throughout the luteal phase to make it receptive to the implanting embryo.

There seems that, the use of short or long acting preparations of GnRH analogue (GnRH-a) may have a prolonged adverse effect on the function of corpus luteum. Most protocols using GnRH-a, mention that luteal support with either P, hCG or both may be beneficial (4-6).

The midluteal decline in sex steroids (estradiol, P, hCG) may adversely affect implantation. Corpus luteum dysfunction may be the underlying cause of certain early embryonic losses (7).

When LHRH analogue is stopped on the day of the ovulation inducing hCG injection, the LH level remains undetectable for the following 10 days and is lower

than the values in a control group for at least the next 6 days. It was noticed that after the injection of hCG, a rapid fall in P and E2, 8 days after the injection of hCG and a delay in endometrium maturation occurred (8).

In IVF, endometrial maturation is abnormal in up to 75% women and in women who do not conceive both the P level and P/E2 ratio are lower at the beginning of the luteal phase. For these and other reasons luteal phase support may be beneficial in IVF. However, until now the benefit of this support has rarely been objectively demonstrated.

MATERIALS AND METHODS

The study included infertile women undergoing IVF-ET during a year in Dr. Zekai Tahir Burak Reproductive Endocrinology and IVF Unit. Patients above 40 years of age were excluded since the ongoing pregnancy rate and the total abortion rate may be different from the rates of patients <40 years of age. One hundred and fifty seven cycles were performed between those months. Of these 157 cycles, in 143 of them oocyte pick-up and in 108 of them embryo transfer were performed. 7 patients with the risk of ovarian hyperstimulation syndrome (OHSS) were excluded as in these cases we prefer to give progesterone for luteal support on purpose.

We used long protocol for hormonal suppression. Buserelin (Suprefact proinjection flacon, HOECHST) 0.5 mg s.c. was administered starting from the day 20 of the previous cycle. Ovulation stimulation was achieved with pFSH, hMG (Metrodin, Pergonal; Serono laboratories, Istanbul). Monitoring in both groups consisted of daily serum E2 level and follicular measurement by transvaginal ultrasound. When E2 levels reached or exceeded 400pg/ml per follicle and when follicle exceeded 1.5 cm in the largest diameter, 10.000 IU, hCG (Pregnyl, Organon, Turkey) was given intramuscularly. Oocyte recovery was scheduled for 36 hours later.

Oocyte recovery was achieved transvaginally. They were inseminated with conventional methods. Each gamete was inspected for evidence of fertilization 18 hours after insemination. The presence of two or more pronuclei was considered as evidence of fertilization. Only normally fertilized ova were transferred in Ham's F-10 medium in supine position transcervically about 48 hours after recovery. Clinical pregnancies which were defined by a sac at ultrasound, were used for pregnancy rate calculations. Ongoing pregnancies have been classified as those >6 months gestation with a live fetus.

In this retrospective study 2 groups were identified. Group I; consisted of hCG supplemented group involving 35 patients during the luteal phase. They were started 1500 IU hCG (Pregnyl, Organon-Turkey) on the day before the embryo transfer and 6 times for every 3 days. Group II, included 54 patients who were given progesterone in oil 50 mg/day for 20 days starting a day before embryo transfer. Every pregnant patient received hydroxyprogesterone caproate until 12 weeks 500 mg weekly.

Estradiol and P, FSH, LH concentrations were measured by radioimmunoassay (Diagnostic products Inc., USA) The interassay and intra-assay coefficient of variation for E2 was 11.1% and 9.2%, for P, 11.0% and 8.4% respectively and 3.4% and 2.0% for FSH and LH.

Statistical analysis was performed by using Student's t test and chi square test.

RESULTS

Data from 2 groups showed that they were similar concerning patient and treatment characteristics. There was no statistically significant difference between the 2 groups from etiological point of view. They did not differ in the number of oocytes retrieved, total number of embryos, total number of hMG ampoules, used. The groups exhibited similar E2, P and endometrial thickness on hCG day (Table I).

Of the 35 patients in Group I, 9 conceived. Of the 54 patients in Group II, 10 got pregnant (Table II). The overall pregnancy rate was 19%, below 40 years of age.

In the first group, 6 of 9 pregnant patients aborted in the first trimester, only 3 delivered. In Group II 4 of 10 pregnant patients aborted in the first trimester, only 6 delivered.

There was no statistically significant difference in pregnancy rates between the 2 groups (chi-square test, Yates corrected). When hCG group and P group as a whole compared, again there was no statistically significant difference (chi-square test, Yates corrected, p:0.322) from abortion point of view, hCG group had a trend to abort more frequently than the progesterone group as a whole (Fischer's exact test; p=0.06).

Table I. The characteristics of the hCG and P in oil group

	Group I hCG (n:35)	Group II P in oil (n:54)
Age (years)	33.3 ± 4.9	33.4 ± 3.9
Tubal factor	17	25
Male factor	6	13
Unexplained	8	10
Others	4	6
E2 on hCG day	1869 ± 670	1624 ± 795
P on hCG day	1.3 ± 0.4	1.1 ± 0.6
Endometrial thickness (mm) on hCG day	10.5 ± 2.6	11.2 ± 2.0
Number of oocytes retrieved	7.4 ± 5.0	6.7 ± 3.4
Total no of embryos	4.3 ± 3.5	4.1 ± 2.7
Total no of hMG ampoules	36 ± 14	36 ± 18
Fertilization Rate (%)	64.9 ± 30.9	70.3 ± 33.5

* Chi-square was used for statistical purposes.

Table II. The pregnancy rates of hCG and P in oil group

	Group I hCG (n:35)	Group II P in oil (n:54)
Pregnancy	9	10
** Abortion	6	4
Ongoing	0	0
Delivery	3	6
Pregnancy rate	24.3	23.6

*Chi-square was used for statistical purpose.
** Fischer's Exact Test p: 0.06

DISCUSSION

Luteal phase support is more important in IVF cycles in which GnRH-a is used because of the poor development of the corpus luteum. The luteal phase of IVF-ET cycles has come under great scrutiny as the cause for the discrepancy between fertilization rates and pregnancy rates. Some theories have been proposed to account for the apparently suboptimal peri-implantation hormonal environment. It may be because of the sequelae of the ovulation induction regimens employed in IVF which may cause high E2 levels with an adverse environment (7,9). Follicular aspiration during oocyte pick-up may lead to removal of a sufficient mass of granulosa cells which may cause luteal phase inadequacy (10). Besides it may be a result of aberrant embryogenesis, additionally any invasive procedure may result in compromised blood frow to the manipulated area there by preventing hCG from reaching its target.

GnRH-a use, in IVF cycles causes a suppression of gonadotropins in luteal phase also thereby causing a decrease in progesterone which remains higher in conception cycles. In conception and nonconception cycles whether follicular stimulation was achieved with hMG or pfSH a midluteal decline in E2 and P levels was observed (11).

Efforts to improve endometrial receptivity and pregnancy maintenance during IVF cycles have not resulted in any generally accepted regimen. In certain studies it was shown that by using multiple doses of 1000-2000 IU hCG during the luteal phase, corpus luteum life span was prolonged, luteal phase P levels, P:E2 ratio was increased (12,13). Some authors reported better results with P supplementation during luteal phase. However, in most of the studies though it was shown that corpora lutea of potential biochemical pregnancies have been rescued, leading to healthy gestations improving the pregnancy rate, however statistically significant difference accomplishment necessitates the consideration of larger number of cycles.

In a meta-analysis of randomized trials of this subject, using P in IVF patients with or without GnRH-a, in luteal phase shows a small but significant increase in pregnancy rates (3). The effect of hCG in IVF where GnRHa is part of the protocol, is much greater and this treatment improves the odds of pregnancy approximately fourfold. However, because of the significant haterogeneity of treatment effect and as it increases the OHSS risk, it was not supported to use hCG in all IVF patients by the existing data. Vaginal application of progesterone suppositories may be considered as an alternative to these treatment modalities.

In this retrospective, randomized study, the comparison of results showed no significant difference between the groups from the pregnancy rate point of view, both when the progesterone group was compared to the hCG group (p: 0.322, Yates corrected) contrary to the literature.

When the two groups were compared for abortion, no statistically significant difference was detected. However, patients who used hCG in luteal phase and hydroxyprogesterone caproate during the rest of the first trimester, had a trend to abort more frequently compared to ones who used progesterone and hydroxyprogesterone caproate (p:0.06, Fischer's exact test) contrary to the literature.

Luteal support therapy is believed to be a major contributor to the improvement. Though in literature there are publications related to using no luteal supplement in ART, in order to asses a more beneficial effect progesterone needs to be given.

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