Use of Human Chorionic Gonadotropin and Vaginal Progesterone Suppositories For Luteal Phase Support in Gonadotropin-Induced Cycles: A Comparative Study

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OBJECTIVE: To determine the efficacy of luteal phase support with human chorionic gonadotropin (hCG) or micronised progesterone (MP) during exogenous gonadotropin induced cycles.
STUDY DESIGN: A prospective randomised cross over study was performed to evaluate the effects of different luteal phase support treatments. Each women received luteal support either with hCG, (after ovulatory hCG injection, on days 3, 6 and 9, injection of 1500 IU hCG), or with vaginal MP (200 mg vaginal MP progesterone suppository twice a day, starting 3 days after the ovulation triggering hCG injection) or no luteal support in consequent cycles with different orders. Thirty women underwent a total of 83 cycles using gonadotropin for ovulation induction. Groups were compared according to their luteal phase lengths, midluteal progesterone levels, complications, the time of hCG administration and estradiol value at the time of hCG administration.
RESULTS: In the group of hCG luteal support, the midluteal progesterone (MLP) was significantly higher and the luteal phase length was significantly longer compared to MP and control group. Pregnancy rates were not statistically different for the groups.
CONCLUSION: Luteal phase support, during gonadotropin induced cycles, affect luteal phase positively. But, no improvement in pregnancy rates was achieved with the use of luteal phase support.
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Key Words: Luteal support, Progesterone, Pregnancy, Human chorionic gonadotropin

Luteal phase dysfunction (LPD), a postovulatory sequela of aberrant folliculogenesis, is recognised as a defect in progesterone (P) production, reception, or action. It is responsible for an estimated 3 to 4% of infertility cases and 30 % of cases of habitual abortion.[1,2]

Till now, there are so many researches about diagnostic methods, patophysiology, therapy modalities of LPD and how clomiphene citrate (CC) causes LPD. But we don't have enough literatures about the luteal phase dysfunction in gonadotropin cycles. We also don't know whether luteal phase support is necessary or not.

Our study's aim is, to support the gonadotropin cycles by using different luteal phase treatment modalities and to search the effectivity of therapy, complications and variabilities of hormone levels.

Material and Methods

The study was conducted at infertility clinic of Zekai Tahir Burak Women's Health, Education and Research Hos-

pital. The study was approved by the Human Research Committee of our hospital. Patients with clomiphene citrate-resistant anovulation, euprolactinemic hypogonadotropic amenorrhea, tubal factor and unexplained infertility were selected for the study. Thirty women, who were about to undergo gonadotropin therapy, enrolled in the study. The women treated with GnRH agonists were excluded from the study.

Treatment was initiated as our standard protocol. On the 3rd day after menses, a pelvic ultrasound was performed. Two ampules of hMG were then administered intramuscularly (IM) daily. Serum estradiol (E2) and follicular size were determined every 1 to 3 days and the HMG dose adjusted on individual bases until follicular maturation was achieved. This was defined as the presence of at least one follicle 16 mm in mean diameter with E2>300 pg/ml per mature follicle. At this point, each patient was assigned to receive intramuscular (IM) injection of hCG 10 000 IU (Profasi®; Serono). A patient was allowed to enter the study in three consequent cycles with one of the treatment modalities for luteal phase support. In the first group, after ovulatory hCG injection, on days 3, 6 and 9 intramuscular injection of 1500 IU hCG, were administered. In the second group, the luteal support, consisted of two 100 mg vaginal progesterone suppositories (Progestan®; Kocak) twice a day. On the 18th day of the luteal support a pregnancy test was performed. If the test was negative, P suppositories were discontinued. In the case of pregnancy, the suppositories were continued until transvaginal ultrasound demonstrated fetal heart beat 2 weeks later. The third group, was the control group and was applied no therapy.

During the alternate cycles, women were included to the other therapy cycles. In this way, each patient served as her own control.

The duration of the luteal phase was defined as the interval between the hCG and the onset of the next menstrual period not including the day of hCG and the first day of the new period.

On the 8th day of the luteal support, midluteal progesterone was measured. On the 18th day of the luteal support a pregnancy test was performed.

Ovarian hyperstimulation syndrome and cyst formation were accepted as complications.

Serum E2 was determined by radioimmunoassay (RIA). Same methods were used for progesterone and we accepted 10 ng/ml as the normal value of midluteal progesterone. All ultrasonographies were performed with Combison 320-5 using a 5.0 mHz transvaginal sector probe.

We compared the luteal phase lengths, midluteal progesterone values, the time of hCG administration, estradiol value at the time of hCG administration and the complications of the 3 groups.

The Statistical Program for Social Sciences (SPSS) for Windows software was used for the calculations. The statistical methods used were chi-square and Fisher's exact test and ANOVA where appropriate.

Results

Thirty patients with a mean age of 29.47 years and a mean duration of infertility of 4.93 years underwent a total of 83 cycles. Twenty patients were primary infertile, 10 patients were secondary infertile (Table 1).

Table 1. Patients' characteristics

	Mean	Std. deviation	Range
Age	29.47	±4.80	22-39
Infertility Year	4.93	±2.19	1.5-10
Infertility Type:	Patients' numbers	%	
Primary	20	66.7	
Seconder	10	33.3	

Groups were compared according to their luteal phase lengths, midluteal progesterone levels, complications, the time of hCG administration and estradiol value at the time of hCG administration (Table 2).

Mean midluteal progesterone levels were greatest at cycles with supplemental hCG administration (p<0.001). Between micronised progesterone group and the control group, MLP was significantly higher in micronised progesterone group (p<0.001) (Figure 1).

The median luteal phase length was longest in HCG group. And the difference was also statistically significant (p<0.001) (Figure 2).

Ovarian hyperstimulation syndrome and cyst formation were accepted as complications. In MP group, there was no OHSS (0/29); 4 cyst formation (4/29). In hCG group, there was 1 OHSS (1/28) and 6 cyst formation (6/28). In the control group, we had 1 OHSS (1/26) and 2 cyst formation (2/26). But the differences were not statistically significant. (p>0.05) (Table 2).

We had 2 pregnancies in MP group, 3 pregnancies in hCG group and no pregnancies were observed in the control group. The differences were not statistically significant (P>0.05). None of the patients had any complain of about the any of the treatment modalities. All of the women tolerated the I.M. hCG and MP suppositories well.

Discussion

Luteal phase support is routinely prescribed after oocyte retrieval for IVF-ET. A luteal phase deficiency in IVF-ET cycles may result from the use of GnRH agonists for pituitary down-regulation, leading to prolonged LH suppression, or result from poor progesterone production after granulosa cell removal during multiple follicular aspiration.[3] Supplementation with either P or hCG during the luteal phase of IVF-ET cycles may improve pregnancy rates, particularly when a GnRH agonist has been used.[4] A recent meta analysis reported that luteal supplementation with either I.M. hCG or I.M. progesterone significantly improved fertility outcomes compared with no treatment.[5] It was recently reported that hCG in combination with progesterone for luteal support improved pregnancy rate in patients with low midluteal estradiol levels in IVF cycles.[6] A report from Penzias showed that luteal support with vaginal micronised progesterone (MP) gel, provided effective and well tolerated luteal support in IVF cycles.[7]

In non-IVF cycles for example gonadotropin induced cycles, luteal phase support is not used routinely. Perhaps the reason is, the duration of these cycles' luteal phases is longer and the granulosa cells are not aspirated.[8]

Despite the fact that hMG and hCG have been used for ovulation induction for more than four decades, relatively little is known about the luteal phase in these cycles. Although we have doubt about luteal phase dysfunction in gonadotropin cycles, general approach is, there is a dysfunction.[9]

The luteal phase of cycles stimulated with exogenous gonadotropins may be characterised by aberrant hormone levels, altered endometrial development and shortened length.[10,11] Perhaps the reason of luteal phase dysfunction in gonadotropin cycles is, dysfunction of physiologic gonadotropin levels, and differences of estrogen and progesterone levels in induced cycles and all of these reasons affect luteal phase negatively.[12,13]

Luteal phase support with supplemental progesterone or hCG has been recommended to help to correct these problems and this improves pregnancy rates, but the efficacy of such regimens is still controversial.[14]

Table 2. Therapy results

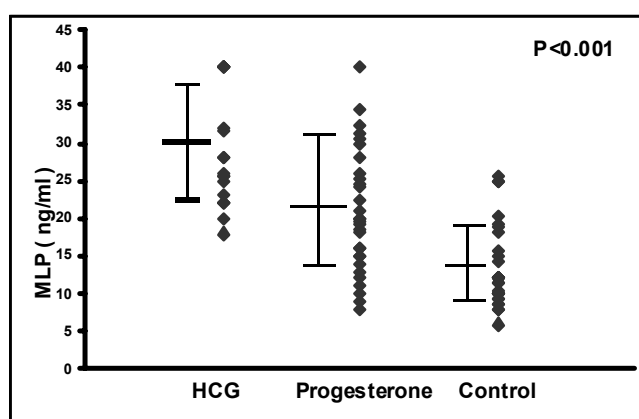|	MP (n=29)	HCG (n=28)	Control (n=26)	P
MLP	21.04±8.23	30.66±8.35	13.02±5.26	P<0.001
LPL (luteal phase lenght)	16.15±3.22	19.40±4.78	13.27±2.47	P<0.001
OHSS	0/29	1/28	1/26	p>0.05
Cyst Formation	4/29	6/28	2/26	p>0.05
Day of HCG	12.76±1.68	13.32±1.68	12.96±1.48	p>0.05
Result (pregnancy)	2/29	3/28	0/26	p>0.05
E2 value at the time of HCG	872.28±302.56	946.71±313.83	777.85±339.	p>0.05

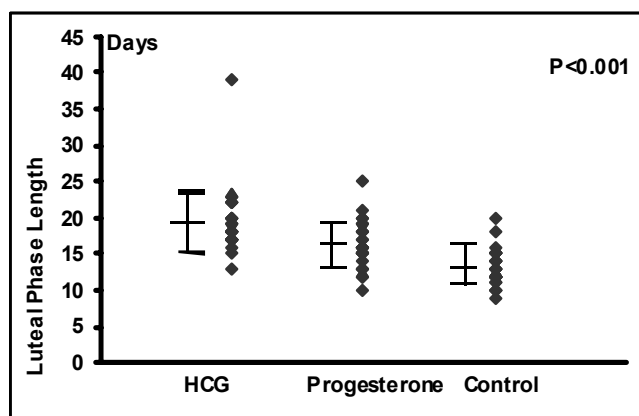Figure 1. MLP levels in cycles.

Figure 2. Luteal Phase Lengths in Cycles.

However, it is also suggested that combination of gonadotropin stimulation with human chorionic gonadotropin result in an inadequate luteal phase with or without the use of exogenous agonists or antagonists.[15]

Blumenfeld and Nahhas reported that pregnancy rate can be improved significantly with repeated hCG supplementation during the luteal phase.[16] Also the abortion rate dropped significantly. Similar results were also reported by Hamilton et al.[17] They concluded that luteal support with vaginal progesterone suppositories increases the pregnancy rates after hMG and hCG induction.

However, Zayed et al. showed that luteal phase support during hMG-stimulated cycles does not lead to improvement in pregnancy rates.[18] Also, Keenan et al reported that luteal phase support with hCG does not improve fecundity rate in human menopausal gonadotropin-stimulated cycles.[14] Hence, they suggested that hCG support of the luteal phase is not routinely warranted in hMG-stimulated cycles.

In our study either hCG or MP groups, mid luteal progesterone levels were higher and luteal phase lengths were longer, especially in hCG groups. And the results were statistically significant. The reason might be the stimulator effect of hCG in corpus luteum and exogenous progesterone might suppress the LH concentration.[19]

Although in natural cycles, the least progesterone level is 10 ng/ml for normal luteal phase, the minimum level for induced cycles is not known clearly today. And also for implantation there is no cut off value of progesterone.

We don't have enough prospective and retrospective studies about luteal phase support in gonadotropin cycles which compare hCG and MP agents each other.

As a conclusion we can say that, luteal phase support in gonadotropin induced cycles, affect luteal phase positively. However, no improvement in pregnancy rates was achieved with the use of luteal phase support.

But we need more studies, which include more people, and homogenous different groups of people to decide whether the luteal support in gonadotropin induced cycles is necessary or not.

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