# Luteal phase support in ovarian induction cycles using human chorionic gonadotropin or oral progestagens

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## ABSTRACT

**Objective:** To determine the efficacy of luteal phase support with human chorionic gonadotropin (hCG) or oral progesterone during human menopausal gonadotropin (hMG) ovulation induction.

**Methods:** Between September 1999 and March 2001, a total of 91 couples with infertility were recruited at Al-Hammadi Hospital, Riyadh, Kingdom of Saudi Arabia and Badeea Hospital, Jordan. In this prospective trial 46 couples were allocated to luteal phase support with hCG injections, while 45 couples were allocated to Duphaston (oral progestogens) as luteal support.

**Results:** In the group of hCG luteal support, 46 patients completed 46 cycles of hMG therapy, and 8 pregnancies (5 ongoing pregnancies) ensued, with a general total pregnancy rate of 17.4%. In the progesterone (Duphaston) luteal support group, 45 patients with the similar indications to the previous group were studied and 8 pregnancies (5 ongoing pregnancies) were reported with a general total pregnancy rate of 17.8%. Only one spontaneous abortion occurred among the patients in a cycle supported with supplemental hCG, while 2 abortions occurred in the Duphaston supported group.

**Conclusions:** Despite theoretical reasons to use luteal phase support during hMG-stimulated cycles, our data showed no improvement in pregnancy rates from such treatment.

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Inspite the widespread use of human menopausal gonadotropins (hMG) for induction of ovulation and recruitment of many follicles for assisted conception techniques, those cycles' luteal phase remain enigmatic. A lot of data has been accumulated describing alterations in endometrial dating, cycle length, and hormonal patterns.[1,2] Despite the lack of universal agreement on the nature and significance of luteal phase abnormalities in hMG-stimulated cycles, there is general acceptance that luteal phase deficiency may exist.[3] Midluteal decline in sex steroids is seen with lack of luteal support, which adversely affects implantation.[4] This has led to the use of luteal phase support with progestational agents or human chorionic gonadotropin (hCG) in attempts to correct such defect to improve the pregnancy rates, specially in vitro fertilization-embryo transfer (IVF-ET) cycles despite a lack of evidence of this alleged efficacy. Both regimes of luteal support for example progesterone or hCG, have different modes of action. Progesterone is a direct form of luteal support the end product of corpus luteum, but hCG is an indirect form of luteal support. Although progesterone seems the optimal form of luteal support,[5] a meta-analysis performed by Soliman et al[6] established a beneficial effect of hCG in particular. The

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use of luteal phase support during conventional (for example non-IVF) ovulation induction with hMG has been less frequent. The luteal phase of such cycles may vary from those of IVF-ET cycles due to no aspiration of granulosa cells. Blumenfeld and Nahhas et al,[7] Messinis et al[8] have noted higher pregnancy rates during ovulation induction with hMG when luteal phase support was administered with hCG. However, a valid question has been raised concerning the methodologies used in these investigations.

Therefore, we performed this study to determine the efficacy of luteal phase support with hCG or oral progesterone during hMG ovulation induction.

**Methods.** Between September 1999 and March 2001, a total of 91 couples with infertility were recruited at Al-Hammadi Hospital, Riyadh, Kingdom of Saudi Arabia and Badeea Hospital in Jordan. None of the women had previous assisted reproductive technology treatments; all were <40-year-old, with a minimum duration of infertility of 2 years. They had bilateral tubal patency, which had been confirmed with a recent laparoscopy or hysterosalpingogram. The couples according to the planned luteal phase support were allocated into 2 treatment supports using hMG for ovarian induction with intrauterine insemination (IUI) groups. In this prospective trial 46 couples were allocated to luteal phase support with hCG injections, while 45 couples were allocated to Duphaston (oral progestogens) as luteal support.

***Treatment plan.*** The basal blood tests for plasma, follicle stimulating hormone (FSH), and luteinizing hormone (LH) concentrations, were performed on day 2 of the cycle (measurement of FSH and LH were performed; after the patient had given information regarding her last menstrual period. Ovulation was induced if both FSH and LH concentrations were less than 10IU/L hMG ampoules were given starting from day 3. Patients attended the clinic on day 7 for a plasma E2 estimation and ultrasound examination was arranged to check follicular growth and accordingly, hMG was given intramuscularly (IM) in doses of 75 IU daily. On day10 patients attended for a plasma E2 estimation and ultrasound to assess follicular growth. They continued hMG administration daily, monitored with pelvic ultrasound then on alternate days an ultrasound examination was carried out and plasma LH concentrations were estimated. The dose of hMG was individually adjusted to the ovarian response until the time of IUI, at most 3 follicles more than 18mm mean diameter were achieved with a plasma concentration measurement of at least 1000 pmol/l of E2 for each follicle. Human chorionic gonadotropin 10,000 IU was then given and IUI was planned with the husband's prepared semen (Percoll's gradient or swim up ) after 34-36 hours. Patients in both groups were given luteal support with hCG 5000 iu IM twice weekly, or oral progesterone tablets (Duphaston) orally from d1 after IUI until an estimation of plasma hCG was performed on day 14.

**Table 1 -** The comparison between the 2 groups of luteal support.

| Parameters | Duphaston (Progesterone group) | hCG group |
|---|---|---|
| Mean age (years) | 31.8 | 32.3 |
| N | 45 | 46 |
| Ampules N | 12.6 | 11.6 |
| Follicles >18mm | 1.4 | 1.6 |
| hCG time | D 11.5 | D 11.7 |
| Endometrial thickness at hCG time | 9.1mm | 8.9mm |
| ***Outcome*** | 5 | 5 |
| Pregnancy | 2 | 1 |
| Abortion | 1 | 2 |
| Biochemical | | |
| **Total** | **8** | **8** |

hCG - human chorionic gonadotropin

The data analyzed included all pregnancies (clinical, abortion, ectopic, and biochemical). Implantation was considered to have occurred if the plasma hCG concentration rose above 10 U/L and all clinical pregnancies were determined by detecting an intrauterine gestational sac with positive fetal heart on an ultrasound scan.

**Results.** **(Table 1)** In the group of hCG luteal support 46 patients with a mean age of 32.3 years were studied, their mean duration of infertility of 40 months completed 46 cycles of hMG therapy. Indications for treatment included anovulatory, mild male factor, and unexplained factor infertility. Eight pregnancies (5 ongoing pregnancies ensued, with a complete total pregnancy rate of 17.4%. In the progesterone (Duphaston) luteal support group, 45 patients with a mean age of 31.8 years were studied with similar indications in the previous group. Eight pregnancies (5 ongoing pregnancies) were reported with a complete total pregnancy rate of 17.8%. The number of preovulatory (for example 18 mm mean diameter) follicles present at the time of hCG injections was slightly greater in the hCG supported cycles (1.6 versus 1.4). The number of ampules of hMG used were 11.6 in hCG group versus 12.6 in the Duphaston group, the endometrium thickness was 8.9mm in the hCG group while it was 9.1mm in the Duphaston group. Only one spontaneous abortion occurred among study patients, in a cycle supported with supplemental hCG. while 2 abortions in the Duphaston supported group.

***Statistical analysis.*** Statistical analysis was carried out using Student's t-test, Mann-Whitney test when appropriate, on discrete results chi square ($X^2$) was used

and Fisher's exact test when appropriate. The differences were considered significant at a level of $P<0.05$.

**Discussion.** Many abnormalities of the luteal phase following hMG therapy have been described. These include a shortened luteal phase, abnormal endometrial development, and aberrant hormone profiles; which may contribute to the relatively low pregnancy rates. This problem has led to the development of various regimens to help support the luteal phase. Studies evaluating luteal phase hCG supplementation have shown conflicting results.

It has been suggested that IVF patient may lose their pregnancies due to poor luteal phase function (resulting from removal of granulasa cells during oocyte retrieval) and a further suggestion that high serum E2 concentration achieved in stimulated cycles may act against implantation, so luteal support is encouraged and used routinely after oocyte retrieval for IVF in some centres. this approach is based on earlier observations in IVF cycles that a significantly higher progesterone level was found to correlate with pregnancy.[9-11] Daya[12] in his meta-analysis did not support the routine use of progesterone in IVF cycles in which ovarian stimulation was achieved with cc and hMG, while in his meta-analysis Soliman et al[6] found that the use of hCG is beneficial in GnRH-a cycles of IVF and superior than progesterone. Our study does not show any significant difference in the pregnancy rates when supplemental hCG or Duphaston were used in the luteal phase after ovulation induction with hMG. A possible explanation is that neither hCG nor Duphaston adequately restores normal luteal function, or the luteal phase is not a significant factor in lowering cycle fecundity during hMG therapy. We should also consider that this study is using relatively a small number and may be did not reach the power to differentiate between both luteal support. Numerous studies on this subject have been published since the original description of an hMG associated luteal phase defect by Edwards et al.[13] Some studies have specially evaluated luteal phase support with hCG during hMG ovulation induction. Messinis et al[8] noted increasing pregnancy rate in women in World Health Organization (WHO) group I anovulatory infertility when given supplemental hCG, but not in WHO group II patients. Blumenfeld and Nahas,[7] who also noted an increased pregnancy rate during cycles with supplemental hCG administration. However, Keenan and Moghissi[14] concluded that hCG support is not routinely warranted in hMG stimulated cycles. Therefore, despite theoretical reasons to use luteal phase support during hMG-stimulated cycles, our data showed no improvement in pregnancy rates from such treatment. Several factors may account for this. First, we believe that it is important to induce ovulation with 10,000 iu hCG to compensate for any early depression of serum LH levels. Secondly, shortening of the luteal phase and other indicators of luteal phase deficiencies are found in relatively few patients. Therefore, although this subset of patients may well benefit from luteal phase support therapy, it may be difficult to document.

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