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# LOW DOSE HCG IN PREVENTING OHSS IN HIGH-RISK WOMEN

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**Introduction:**

Ovarian hyperstimulation syndrome(OHSS) is a complication of fertility treatment, which uses pharmacological ovarian stimulation to increase the number of oocytes and therefore embryos available during assisted reproductive technology (ART).Severe ovarian hyperstimulation syndrome (OHSS) is well known to be a rare but potentially fatal condition in anovulatory women with polycystic ovarian syndrome (PCOS) when undergoing IVF. Low-dose stimulation is thus recommended, but it can still lead to ovarian hyperstimulation associated with high serum oestradiol concentrations by the time leading follicles reach maturity. Several methods have, therefore, been applied to prevent OHSS. First, risk assessment is made on the basis of the previous history of OHSS and the identification of women with PCO. Second, in treatment cycles a high concentration of oestradiol and three ultrasound parameters (i.e. high number of follicles, large ovarian volume, and high stromal vascularity) on the day of human chorionic gonadotrophin (HCG) are all predictive of increased risk of developing OHSS.

Under these circumstances, various methods have been adopted to prevent the development of OHSS. Abandoning cycles prior to administration of HCG or proceeding with egg collection and freezing all embryos is an inefficient method of management of treatment cycles. Another approach is to withhold FSH to reduce oestradiol concentrations (coasting), which acts through the down-regulation of vascular endothelial growth factor (VEGF) gene expression .Coasting up to 3 days can prevent OHSS but yields inferior pregnancy rates .

Ovulation induction with HCG in infertile patients is likely to remain the method of choice despite the availability of recombinant LH. A survey of the literature and data from various clinics indicate that there is wide variability (5000–25,000 IU) in the dose of HCG for ovulation induction, although there appears to be little evidence to support the use on any particular dose concentration. Individual clinics appear to have selected a dose of HCG on an arbitrary basis to ensure that as many follicles as possible are ovulated and that there is a successful pregnancy outcome following embryo transfer. This study was designed to find out whether the incidence of OHSS could be reduced without compromising the outcome of IVF cycles by lowering the ovulatory dose of HCG to 2500 IU.

**Materials And Methods**

Women at high risk of severe OHSS on the day of HCG administration were offered three choices; abandonment of cycle, coasting or low- dose HCG. Patient information included the impact of HCG on OHSS and different dosages (10,000, 5000 and 2500 IU) used in accordance with ovarian response and the risk of OHSS. Patients were also given full counselling as to the different management options. All women who consented to lowdose HCG were included in this study. They had received a daily dose of 100 IU FSH or 112.5 IU FSH in a first attempt or 150 IU FSH in a second attempt (based on previous response) in a long pituitary down- regulation protocol.

HCG was administered when the mean diameter of the leading follicle 16-20mm size. In all cases, the following characteristics were recorded at the time of HCG administration: (i) there were 4–5 follicles >16 mm and more than 20 follicles in total in each ovary; (ii) serum oestradiol concentrations were >14,000 pmol/ l on the day of HCG administration; (iii) both ovaries had high volumes (combined volume >184 ml); (iv) there was high ovarian vascularity, as subjectively assessed by examining power.

Women exhibiting the above four criteria were given 2500 IU HCG (half of an ampoule of 5000 IU) subcutaneously and follicle aspiration was planned 34–36 h after HCG administration. All follicles were aspirated.

Embryo transfer was performed either on day 3 or 5, depending on the available embryos as per the protocol of the laboratory. A maximum of two embryos was transferred. Any good quality spare embryos were frozen.

Progesterone supplements in the form of cyclogest vaginal pessaries (400 mg twice daily) were given for luteal support. All women were followed up with during the luteal phase regarding their well-being and serum -HCG was carried out 2 weeks after embryo transfer to check for pregnancy.

**Results**

In total, 26 women, aged between 28 and 36 years and at risk of developing severe OHSS, received 2500 IU HCG. Eight of them had developed severe OHSS in a previous IVF attempt, including one woman who had developed an arterial thrombotic episode with an ovulatory dose of 5000 IU HCG and she was treated with heparin. The mean duration of stimulation was 8.6days. The mean number of total follicles was 39(22–56) and, of those, 13 were greater than 14 mm. The combined minimum ovarian volume was 188ml.

Assessment of ovarian vascularity by power Doppler ultrasound showed high stromal vascularity with colour signals from all follicles greater than 12 mm. The total dose of FSH used per cycle ranged between 750 and 1650 IU per woman. The range for serum oestradiol was between 14,445 and 27,669 pmol/l on the day of HCG. Four women whose oestradiol concentrations were greater than 30,000 pmol/l were coasted for 3 days and their oestradiol concentrations were still above 20,000 pmol/l prior to HCG administration (Table). The mean number of oocytes collected was 29 (range 11– 32) . No woman developed moderate or severe OHSS and only one woman developed symptoms of mild OHSS.Table Serum oestradiol concentrations in 26 women at high risk of OHSS:

**Table Serum oestradiol concentrations in 26 women at high risk of OHSS:**

| Oestradiol range (pmol/l) | No. of women |
|---|---|
| 14,000–16,000 | 13 |
| 16,000–21,000 | 4 |
| 21,000–26,000 | 5 |
| 26,000–31,000 | 2 |
| 31,000–40,000 | 2 |

## Discussion

OHSS is associated with significant physical and psychological morbidity and has been associated with maternal death. However, in most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution. Women with more severe OHSS require inpatient treatment to manage the symptoms and to reduce the risk of further complications. The induction of ovulation by the controlled administration of an ovulatory dose of HCG is integral to successful IVF for both conventional IVF protocols and the newer natural cycle IVF protocols. The use of HCG as a natural analogue of LH to induce ovulation takes advantage of particular pharmacokinetic properties that give HCG a longer circulating half-life than LH. The longer half-life of HCG means that it persists in the circulation well after ovulation and in this respect it is unlike LH, which is rapidly cleared from the circulation after the LH surge .The persistence of HCG in the circulation is thought to be favourable to the development of a fully competent corpus luteum capable of supporting implantation and normal embryo development following embryo transfer . However, the persistence of HCG is also associated with OHSS, a less desirable side effect that, if left untreated, can be potentially life threatening.

There are strong positive associations between plasma concentrations and follicular fluid concentrations of VEGF and OHSS. The role of VEGF in the pathogenesis of OHSS appears to be due to its ability to increase vascular permeability . Normally, this effect of VEGF leads to paracrine-mediated 'leakiness' of the local vasculature required for late pre-ovulatory follicular enlargement. However, when a large number of mature follicles (greater than 20 in each ovary) are present as a result of exogenous FSH stimulation, there can be overproduction of VEGF and excessive increases in vascular permeability that lead to OHSS.

The serum concentration of VEGF during FSH treatment is not a reliable indicator of OHSS whereas the serum concentration of VEGF after HCG is a good indicator of OHSS. Both LH and HCG stimulate production of VEGF. In vitro, HCG increased VEGF production by cultured granulosa lutein cells and endothelial cells , while in vivo, HCG increases serum concentrations of circulating VEGF and the concentration of VEGF in antral fluid. One of the actions of VEGF is increased vascular permeability and the use of excessively high doses of HCG to induce ovulation, particularly when there has been a good follicular response to FSH, will lead to high secretion of VEGF from the granulosa cells and an increased risk of OHSS.

Three of the criteria that were used to define a high risk for OHSS are well established in the literature. Higher oestradiol concentrations, a higher number of follicles and a significantly higher ovarian volume prior to theadministration of HCG have been found in women who developed moderate to severe OHSS compared with women with mild or no complications. Increased stromal vascularity reflects increased angiogenic activity and VEGF concentrations and the fourth criterion of risk was the finding of high stromal vascularity on power Doppler examination.

This pilot study revealed two important findings. Firstly, at this dose of HCG, no moderate or severe OHSS was observed in these 21 women who were at high risk of severe OHSS. Secondly that a dose of HCG as low as 2500 IU will mature FSH stimulated follicles. Comparing the number of follicles seen by ultrasound examination with the numbers of oocytes recovered, fertilized and successfully implanted none of the critical post-ovulatory processes involved in IVF appeared to be impaired by this dose of HCG.

To allow the conclusion that a lower dose of HCG is the treatment of choice in high risk patients at the present time, nevertheless it is possible to conclude that a low dose of HCG is less likely to cause OHSS because there is less VEGF produced by granulosa cells even when there has been a high level of FSH-stimulated follicle development as VEGF reduces risk of excessive increase in vascular permeability.

## Conclusion

The evidence from this pilot study is that, in women at high risk of OHSS, a reduction of the current 'minimum' dose (i.e. 5000 IU) of HCG to 2500 IU appears to prevent the development of OHSS in these women without compromising success rates.

Further studies are needed to establish the minimal ovulatory dose of HCG and LH required in the management of IVF cycles.

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