

PREVENTIVE MEASURES OF OVARIAN HYPERSTIMULATION SYNDROME

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ABSTRACT

Objective : To review the up-to-date randomized controlled trials (RCT) & meta-analyses concerning prevention of ovarian hyperstimulation syndrome (OHSS).

Designs : An electronic search of the Cochrane library, Pub Med for RCT & meta-analyses concerning OHSS from 1990 to 2005.

Results : Six Cochrane systematic reviews, 4 meta-analyses & 28 RCT were reviewed as regarding choice of the treatment regimen, preventive measures on the day of human chorionic gonadotropin (HCG), on the day of oocyte retrieval, at the time of embryo transfer & during the luteal phase.

Conclusions : 1. Laparoscopic ovarian drilling & use of urinary follicle stimulating hormone (uFSH) rather than human menopausal gonadotropin (HMG) in stimulation cycles without concomitant use of a GnRh-a are associated with reduction of OHSS in polycystic ovary syndrome (PCOS). 2. Significant reduction in incidence of OHSS is observed with low dose step up FSH protocol. 3. Recombinant luteinising hormone (rLH) results in a highly significant reduction in OHSS compared to urinary luteinising hormone (uHCG). 4. Use of gonadotropin releasing hormone agonist (GnRHa) instead of HCG in antagonist protocol is associated with reduction of OHSS. 5. There is insufficient evidence to determine if coasting is an effective strategy for preventing OHSS. 6. Administration of human albumin is not effective in reduction of severe OHSS. 7. Given the increased risk of OHSS associated with HCG, intramuscular (IM) progesterone is favored for luteal phase supplementation.

Keywords : Ovarian hyperstimulation syndrome, controlled ovarian hyperstimulation, assisted reproductive technologies.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproductive technology; so prevention is the most important tool for patient safety.

There are divergent opinions regarding the effective strategies for prevention of OHSS. Different strategies for prevention of OHSS are known. Before starting controlled ovarian hyperstimulation (COH), patients at high risk for OHSS should be identified & the appropriate

treatment regimen is selected. Risk factors developing during COH should be detected & preventive measures are taken on the day of HCG, on the day of oocyte retrieval, at the time of embryo transfer & during the luteal phase.

A. Choice of the treatment regimen

1. In PCOS:

- a. Ketoconazole does not prevent OHSS in patients with PCOS who are undergoing ovarian stimulation. It may reduce the rate of folliculogenesis and steroidogenesis⁽¹⁾.

- b. Laparoscopic ovarian electrocautery is a useful treatment for women who have previously had an IVF cycle cancelled due to risk of OHSS or who have suffered OHSS in a previous cycle⁽²⁾.
- c. HMG Vs uFSH : There is a reduction in the incidence of OHSS with uFSH compared to HMG in stimulation cycles without concomitant use of a GnRh-a⁽³⁾.
- d. HMG/FSH alone Vs GnRHa plus FSH/HMG: An increased risk of OHSS associated with GnRHa use⁽⁴⁾.

2. Method:

- a. Antagonist Vs agonist: No statistically significant reduction in incidence of severe OHSS⁽⁵⁾.
- b. Cetrorelix Vs ganirelix: Cetrorelix but not ganirelix reduce the incidence of OHSS⁽⁶⁾.

3. Protocol

Ultrashort Vs long Protocol: Lower rate of OHSS in ultrashort protocol than in the long one⁽⁷⁾.

4. Gonadotrophin:

a. Dose

- i. Gonal F: 150 IU Vs 225 IU: Incidence is higher with 225 IU⁽⁸⁾.
- ii. Puregon: 100 Vs 200 IU: The incidence of OHSS is higher in the high dose group⁽⁹⁻¹¹⁾.

b. Regimen

- i. Low dose step up FSH Vs conventional FSH protocol: Significant reduction in incidence of OHSS was observed in the low dose group⁽¹²⁾.
- ii. Chronic low dose Vs conventional rFSH: No difference in OHSS⁽¹³⁾.

- iii. Conventional Vs personalized protocol: A personalized regimen based on body mass index (BMI) & waist/hip ratio is not associated with any significant increase in severe OHSS⁽¹⁴⁾.

c. Type:

- i. Highly purified (HP)- HMG Vs rFSH: The incidence of OHSS was similar in both treatment groups^(15,16).
- ii. HMG Vs rFSH: No difference⁽¹⁷⁾.
- iii. rFSH Vs uFSH: No difference^(18,19).
- iv. Gonal F Vs puregon : The incidence of OHSS was similar⁽²⁰⁾.

d. Monitoring:

Ultrasound versus ultrasound and hormonal levels: Pregnancy and OHSS rates were similar (34.3% vs. 31.4% and 4.9% vs. 4.1%, respectively)⁽²¹⁾. The addition of estradiol (E2)/follicle criteria to ultrasound monitoring of IVF cycles in normal responders seldom changes the timing of HCG, and does not increase pregnancy rates or the risk of OHSS.

B. On the day of HCG

1. Rec LH Vs uHCG: Rec LH is effective in inducing final follicular maturation & is comparable with uHCG. Rec LH results in a highly significant reduction in OHSS compared with uHCG.^(22,23) The dose of rLH giving the highest efficacy to safety ratio was between 15.000 & 30.000 IU.

2. Coasting Vs early unilateral follicular aspiration: There was no difference in the incidence of moderate & severe OHSS & in the clinical pregnancy rate between the groups⁽²⁴⁾. Compared with elective unilateral follicular aspiration (elective aspiration of excess ovarian follicles),

there was no convincing benefits associated with the use of coasting. There is a lack of RCT for comparing coasting with no coasting or other interventions such as embryo freezing or intravenous albumin infusion for prevention of OHSS. There is insufficient evidence to determine if coasting is an effective strategy for preventing OHSS.

3. Unilateral ovarian early follicular aspiration prior to HCG administration does not reduce the occurrence of severe OHSS in women at risk (25,26).

4. HCG Vs agonist in triggering final oocyte maturation in antagonist protocol: With GnRH agonist instead of HCG in IVF cycles dramatically decreases luteal levels of inhibins reflecting significant inhibition of the corpus luteum function (27). This may explain the mechanism of OHSS prevention by the use of GnRH agonist.

C. On the day of oocyte retrieval

1. IV albumin: Meta-analysis demonstrated significant reduction in severe OHSS on administration of human albumin at the time of oocyte retrieval in high risk cases (28). Eighteen women at risk needed to be treated with albumin infusion in order to prevent a single case of severe OHSS. This needs to be taken into account in the context of clinical decision making. On the other hand, Ben-Chetrit et al, (29) reported that albumin has no positive effect on OHSS or conception rates, while its use carries the risk of undesirable side effects, including exacerbation of ascites in OHSS, nausea, vomiting, febrile reaction, allergic reaction, anaphylactic shock and risk of virus transmission. They suggested that this form of treatment should not be included in the prevention of OHSS. Albumin infusion on the

day of oocyte retrieval is not a useful means of preventing the development of moderate-severe OHSS (30).

2. IV hydroxyethyl starch: Administration of 6% hydroxyethyl starch prevents the development of moderate-severe OHSS in high risk patients (31).

3. Albumin Vs starch: Both significantly reduced the incidence of OHSS, but starch is a cheaper & safer alternative to human albumin (32).

4. Albumin Vs high dose of progesterone: IM progesterone (200 mg/day) & 100 ml of 20% IV albumin are effective in preventing OHSS (33).

5. Glucocorticoids: Administration of glucocorticoids (Hydrocortisone 100 mg IV, immediately after oocyte retrieval followed by prednisolone 10 mg two times a day for 3 days & 10 mg/d for 2 days) to high risk patients did not reduce the rate of OHSS after ovarian stimulation for IVF (34).

D. At the time of embryo transfer

1. Transferring a single zona-free day 5 embryo (blastocyst) & freezing of the supernumerary embryos offers the patient at risk of OHSS an optimal chance for a singleton pregnancy, while avoiding the serious maternal complications of OHSS (35).

2. Elective cryopreservation of all embryos: A systematic review has found that there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS, for elective cryopreservation versus intravenous albumin or elective cryopreservation versus fresh embryo transfer (36).

E. Luteal phase support

1. HCG Vs progesterone. A recent meta-analysis reported no fertility difference when comparing IM progesterone with HCG (37). Given the increased

risk of OHSS associated with HCG, IM progesterone is favored for luteal phase supplementation.

2. Progesterone (P) alone Vs progesterone combined with HCG: More cases of OHSS were found in the P/HCG group. Vaginal P alone provides sufficient luteal support in GnRHa/HMG induced IVF cycles⁽⁴⁸⁾.

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