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Original Article

Severe ovarian hyperstimulation syndrome: Can we eliminate it through a multipronged approach?

Lt Col Nikita Naredi [a,*], Col S.K. Singh [b], Col Prasad Lele [c], Lt Col N. Nagraj [d]

[a] Classified Specialist (Obst & Gynae) & IVF Specialist, Assisted Reproductive Technology Centre, Command Hospital (Southern Command), Pune 411040, India
[b] Classified Specialist (Obst & Gynae), Command Hospital (Southern Command), Pune 411040, India
[c] Senior Advisor (Obst & Gynae) & IVF Specialist, Command Hospital (Eastern Command), Kolkata, India
[d] Classified Specialist (Obst & Gynae) & IVF Specialist, Assisted Reproductive Technology Centre, Army Hospital (R&R), New Delhi 110 010, India

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ABSTRACT

Background: Prevention of severe Ovarian Hyperstimulation Syndrome (OHSS), a potentially fatal complication of controlled ovarian hyperstimulation has been the aim of all fertility experts. Various pharmacologic and non-pharmacologic interventions have been instituted but the results have been conflicting. These preventive strategies were administered in isolation or as a combination of few aiming to eliminate this iatrogenic sequel. This study aimed to eliminate severe OHSS by multipronged approach incorporating almost all preventive modalities available in patients at high risk for this dreadful complication.

Methods: It was a prospective observational study wherein 112 high risk patients planned for IVF were studied. The multipronged approach was in the form administering calcium gluconate infusion, cabergoline, albumin infusion, GnRH antagonist in luteal phase in addition to elective cryopreservation of embryos. The primary outcome measure was incidence of severe OHSS in the study group and the rate of hospitalisation. The secondary outcome measure was the number of days required for complete recovery and resolution of signs and symptoms.

Results: Out of the 112 high risk patients only one patient (1/112; 0.9%) developed severe OHSS with an overall incidence of 0.095% of severe OHSS in all the cycles. There was no biochemical or haematological derangement in any of the high risk patients.

Conclusion: Although this is the first study evaluating the multipronged approach in preventing the dreaded complication of severe OHSS, it does add to the knowledge that targeting the various pathophysiological pathways at different time frames will bring about prevention of OHSS but further randomised studies may reveal superiority of one intervention over the other.

* *Corresponding author at:*.
E-mail address: nikitanaredi@gmail.com (N. Naredi).
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Introduction

Ovarian hyperstimulation syndrome (OHSS), an iatrogenic and a potentially fatal complication due to an exaggerated response to controlled ovarian hyperstimulation (COH) affects 1–14% of all in vitro fertilisation (IVF) cycles.[1] Of the various grades of OHSS, it is the severe form which is most dreaded and may require hospitalisation too.[2–4] Due to the increase in the usage of Assisted Reproductive Technology (ART) to treat subfertility there has been a concomitant increase in OHSS also. The confidential enquiry into maternal and child health, revealed a figure of three maternal deaths due to OHSS in Netherlands and UK per 100.000 stimulated women and extrapolation of these figures to a global situation would give an even more grotesque number.[5,6]

The pathophysiological hallmark of OHSS characterised by a sudden increase in vascular permeability and increased angiogenesis occurs in response to the ovulation trigger with human chorionic gonadotropin (hCG).[7,8] Various mediators in the form of prostaglandins, the renin–angiotensin–aldosterone system, histamine and inflammatory mediators have been implicated but of all these, vascular endothelial growth factor (VEGF) plays the most pivotal role in its pathogenesis.[8,9]

This complication of ART and measures to treat and prevent it has been intriguing reproductive medicine specialists for decades but no conclusive management protocol to eliminate it has been attained. The treatment has been primarily empirical and prevention has formed the mainstay of management. The preventive strategies aim, to target women at high risk of developing OHSS and institution of various pharmacological and non-pharmacological interventions on them. The pharmacological tools used are: GnRH antagonist protocol during stimulation, albumin infusion, dopamine agonist cabergoline, metformin and the newer ones include calcium gluconate infusion, use of GnRH antagonist (GnRH-ant) after ovum retrieval. The non-pharmacologic modalities are: coasting, cycle cancellation, cryopreservation of oocytes/embryos or use of in vitro maturation.[10,11] Although these measures have not been able to completely eliminate OHSS but have brought about a reduction in its severity.[12]

Various studies instituted preventive strategies in isolation or in combination of the above to prevent this dreadful outcome but to our knowledge, this is the first study conducted wherein a multipronged approach comprising almost all modalities available to tackle severe OHSS has been used. The aim was to investigate the efficacy of multipronged approach in preventing severe early OHSS in high risk patients by administering calcium gluconate infusion, cabergoline, albumin, and GnRH antagonist in the luteal phase in addition to elective cryopreservation of all embryos.

Material and methods

Study design

Institutional review board approval was obtained from the hospital ethics committee. It was a prospective observational study wherein the primary outcome measure was to observe the incidence of severe OHSS in the study group according to the classification of Golan et al.,[13] the rate of hospitalisation and any active interventions like: abdominal paracentesis or pleural tapping following the development of severe OHSS. The secondary outcome measure was to ascertain the number of days required for complete recovery and resolution of signs and symptoms.

The study group

Out of the 1056 patients who underwent IVF during the study period 01 January 2013–31 December 2013, 122 patients were at risk for developing OHSS but 112 of the 122 patients who met the strict inclusion and exclusion criteria were studied and analysed. The inclusion criteria was: known case of polycystic ovarian disease as diagnosed by the Rotterdam criteria (2004), development of 20 or more follicles larger than 11 mm on the day of trigger, serum estradiol (E2) level ≥3000 pg/ml on the day of hCG.[14] The patients were excluded if they had other endocrinopathies like diabetes mellitus, hyperprolactinemia or congenital adrenal hyperplasia or systemic diseases like bronchial asthma or hypertension. If an antagonist cycle was instituted for COH, the patients were not included in the study as GnRH antagonist cycle is not routinely incorporated in our IVF protocol. Although it is known that a GnRH antagonist per se also decreases the severity of OHSS but with large number of cycles being carried out at our centre, it is reserved for selected cases and we wanted to study if we could eliminate severe OHSS in an agonist protocol. In case any one of the treatment protocol was altered the patient was excluded from analysis. In case a patient underwent IVF twice in the study period only one cycle was included.

Stimulation protocol and oocyte retrieval

All 112 patients were administered oral contraceptive pills from the fifth day of cycle followed by GnRH agonist leuprolide acetate 0.5 mg subcutaneously daily from the 21st day. Once down regulation was confirmed both sonologically and by serum estradiol levels (<50 pg/ml), recombinant FSH 75 IU/day or 150 IU/day (Gonal F; Merck Serono) based on AFC and AMH was administered for four days and doses adjusted thereafter as per the ovarian response. Serum E2 levels were measured on the day of trigger. Recombinant hCG (rhCG) 250 μg (Ovitrelle; Merck Serono) was administered if greater than three follicles reached a diameter of 18 mm and ovum pick up (OPU) was done 36 h later. Conventional IVF or intracytoplasmic sperm injection was performed on the retrieved oocytes depending on the couple's history. The embryos were graded on day 3 according to 1–4 scoring system with 1 being the best, which was based on fragmentation, cell symmetry, and blastomere number.[15] Embryo transfer was not done in any of the study group patients and all grade 1 and grade 2 embryos were cryopreserved for future transfer while grade 3 and grade 4 embryos were discarded after informing them. The patients were informed about the status of their embryos and fertilisation failure if any. Patients were fully explained and

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