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Original Article

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

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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.

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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 μ g (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

a written consent was obtained in the beginning. They were told about the stimulation protocol and the possible risks in case severe OHSS developed and presented with the treatment protocol. The high risk subjects were managed on an outpatient basis (OPD) from the day of oocyte recovery with daily clinical and sonological monitoring and hospitalized only if they went into severe OHSS or their clinical condition mandated close supervision. A baseline haematological and biochemical profile on the day of pick up and alternate day thereafter was carried out for the study group as a part of monitoring.

Multipronged intervention

Cabergoline institution

Tablet cabergoline 0.5 mg per day was initiated from the day of ovulation trigger and continued for next eight days.

Calcium gluconate infusion

Calcium gluconate infusion was started after OPU as per the protocol mentioned by Yakovenko et al.¹⁶ It was prepared by dissolving 10 ml of 10% calcium gluconate in 200 ml of physiologic saline and instituted over 40 min. This infusion was administered within 30 min of oocyte retrieval on the day of pickup, day 1, day 2 and day 3 thereafter.

GnRH antagonist administration

GnRH antagonist cetrotide 0.25 mg starting from the day of OPU was administered subcutaneously for next five days.

Albumin infusion

100 ml of 20% albumin was infused to all the subjects during oocyte retrieval.

Elective cryopreservation of embryos

Cryopreservation of grade 1 and grade 2 embryos were carried out on day 3 at 8 cell stage and patients informed. If there was fertilisation failure the same was also communicated to the couple.

Diagnosis of OHSS

OHSS was diagnosed and classified as per Golan's classification.¹³ Mild OHSS was diagnosed in the presence of pelvic discomfort, abdominal distension, nausea vomiting and/or diarrhoea and enlarged ovaries on sonography (5–12 cm). Moderate OHSS occurred in presence of features of mild OHSS plus ultrasound evidence of ascites. Categorisation as severe OHSS required presence of moderate OHSS with clinical evidence of ascites and/or hydrothorax and breathing difficulties. Any derangement in the laboratory parameters: hematocrit levels >45%, white blood cell count >15,000 mm⁻³, serum creatinine 1.0–1.5 mg/ml, and abnormal liver function tests (LFTs) also categorised a patient as severe OHSS. Women were

hospitalized if they had severe OHSS or deterioration in any clinical or laboratory parameter.

Recovery

Recovery was defined if morning hematocrit <40%, no electrolyte imbalance, and normal renal and LFTs during the standardised treatment if there was any derangement. In the event of normal biochemical parameters throughout the monitoring period, the size of the ovaries (ovarian diameter < 6 cm) and absence of any clinical symptoms were taken as recovery.

Statistical analysis

Details of cases were recorded on a structured format and analysed with the help of registered version of Statistical Package for the Social Sciences (SPSS) version 13. Group comparisons were made using Chi square (χ^2) test (for categorical variables) or Student t-test (for scalar variables). Statistical significance was assessed at $P < 0.05$

Results

Out of the 112 women who were considered at high risk for severe OHSS as per the inclusion and exclusion criteria only one lady developed severe OHSS because of clinically tense ascites with breathing difficulty; however she had no laboratory derangements. She required hospitalisation and underwent abdominal paracentesis.

Table 1 depicts the baseline patient characteristics as regards to the mean age, body mass index, the mean period of infertility and the hormonal profile. All the high risk patients had a mean AMH value of 6.5 ng/ml which is itself a predictor of OHSS. The mean serum LH was higher than the mean FSH value (8.4 mIU/ml vs. 5.3 mIU/ml). Of the 112 patients, polycystic ovarian (PCO) morphology on laparoscopy was seen in 40.2% women (45/112), however sonologically PCO morphology was seen in 51.7% of them (58/112).

Table 2 shows the cycle characteristics of the women. The mean dose of gonadotropins used for stimulation was 1245 U and the mean duration of stimulation was 9.9 days.

The incidence of OHSS in the study group is depicted in Table 3. Only one patient (1/112; 0.9%) developed severe OHSS as per the Golan's criteria during the study period of one year.

Table 1 – Demographic profile, hormonal characteristics of the high-risk patients.

Background variables (n = 112)	Mean $\pm$ SD	Median (IQR)
<i>Demographic profile</i>		
Age (years)	27.8 ($\pm$ 2.8)	28.0 (26.0–29.0)
Body mass index (BMI) (kg/m ²)	24.4 ($\pm$ 14.3)	22.7 (21.4–24.9)
Duration of infertility (years)	7.2 ($\pm$ 2.6)	7.0 (5.0–9.0)
<i>Hormonal characteristics</i>		
Baseline FSH (mIU/ml)	5.3 ($\pm$ 2.3)	4.9 (3.7–6.7)
Baseline LH (mIU/ml)	8.4 ($\pm$ 4.3)	7.1 (5.4–9.9)
AMH (ng/ml)	6.5 ($\pm$ 1.2)	6.5 (5.8–7.1)

Table 2 – Cycle characteristics of the high risk women.

Background variables (n = 112)	Mean $\pm$ SD	Median (IQR)
Number of days of stimulation (days)	9.9 ($\pm$ 0.2)	10.0 (10.0–10.0)
Total doses of gonadotropins (IU)	1245.1 ($\pm$ 244.5)	1275.0 (1106.3–1350.0)
Estradiol level (on the day of trigger) (pg/ml)	2621.1 $\pm$ 673.5	2600.0 (2000.0–3087.5)
No of follicles (>18 mm on the day of hCG)	20.7 $\pm$ 3.0	20.0 (18.0–22)
Retrieved oocytes	19.0 $\pm$ 6.3	18.0 (16.0–22.0)
Mean ovarian size (after preventive measures)	9.1 $\pm$ 7.4	8.5 (7.5–9.2)

Table 3 – Grades of OHSS in the study group.

Grade of OHSS	No. of patients	%
No OHSS	19	17.0
Mild OHSS	67	59.8
Moderate OHSS	25	22.3
Severe OHSS	1	0.9

This amounts to an incidence of 0.095% of severe OHSS in all the IVF cycles carried out during the study period.

The primary outcome measure was to evaluate the occurrence of OHSS and elimination of severe OHSS in the high risk group so we clubbed the absence of OHSS and mild grade into one group (Group A), as mild OHSS has been postulated to have no clinical significance and moderate and severe grades in the other group (Group B). All the characteristics were compared in the two groups as elucidated in Table 4. All the features were comparable except the number of retrieved oocytes which was statistically more in the severe group ($P < 0.05$). The other contradictory finding was the maximum ovarian enlargement which was found to be more in the mild group as compared to the severe group (9.3 ± 8.4 vs. 8.7 ± 1.5 cm) which was not statistically significant.

Analysis of the recovery time from OHSS revealed that the subjects who went into moderate and severe OHSS took more time than the mild group however it was not statistically

significant. (7.9 vs. 7.2 days). The mean ovarian size attained overall was 9.1 cm however the ovarian enlargement in Group B women was contradictorily lesser as compared to patient of Group A (8.7 vs. 9.3 cm).

None of the study group women had any haematological or biochemical derangement nor did any of them have complications like venous thrombosis or renal insufficiency. Although the mean recovery time varied from 7.2 to 7.9 days there was a rapid improvement of ultrasound and clinical findings, beginning as early as 4 days after luteal administration of GnRH antagonist in all 112 patients.

Discussion

Efficacy and safety of ART though established, is not without risks, the most serious being, ovarian hyperstimulation syndrome. OHSS may occur in various grades of severity and has been classified variously by different workers. However it is the Golans classification which is followed most frequently. Mild OHSS, not of too much clinical relevance may occur in up to 30% of all IVF patients but it is the severe form which is most dreadful and can be life threatening too.¹⁷ So the prevention of this severe OHSS which has an incidence of 1–3% has been the modus operandi of all fertility centres.¹⁸ In this prospective observational study with an aim to prevent severe

Table 4 – Comparison of demographical, hormonal and cycle characteristics of the two groups.

Variables	No or mild OHSS (n = 86)	Moderate or severe OHSS (n = 26)	p-Value
Age (years) (Mean $\pm$ SD)	27.6 $\pm$ 2.8	28.5 $\pm$ 2.5	0.208
BMI (Mean $\pm$ SD)	25.0 $\pm$ 16.3	22.6 $\pm$ 2.2	0.449
Duration of infertility (Mean $\pm$ SD)	7.1 $\pm$ 2.7	7.4 $\pm$ 1.9	0.561
Baseline FSH (Mean $\pm$ SD)	5.4 $\pm$ 2.4	5.0 $\pm$ 2.2	0.500
Baseline LH (Mean $\pm$ SD)	8.1 $\pm$ 4.0	9.2 $\pm$ 5.1	0.269
Gonadotropins total dose (Mean $\pm$ SD)	1236.3 $\pm$ 232.4	1274.0 $\pm$ 283.9	0.493
Retrieved oocytes (Mean $\pm$ SD)	18.3 $\pm$ 6.4	21.3 $\pm$ 5.8	0.034
No. of days for recovery (Mean $\pm$ SD)	7.2 $\pm$ 1.6	7.9 $\pm$ 2.0	0.094
Maximum ovarian size (Mean $\pm$ SD)	9.3 $\pm$ 8.4	8.7 $\pm$ 1.5	0.711
AMH (ng/ml) (Mean $\pm$ SD)	6.5 $\pm$ 1.0	6.4 $\pm$ 1.8	0.737
Estradiol (Mean $\pm$ SD)	2559.4 $\pm$ 625.4	2825.3 $\pm$ 792.3	0.078
Downregulation (n, %)			
Leuprolide Acetate	59 (68.6)	21 (80.8)	0.229
Triptorelin acetate	27 (31.4)	5 (19.2)	0.766
Laparoscopic findings (n, %)			
Without PCOD	53 (61.6)	14 (53.8)	0.478
With PCOD	33 (38.4)	12 (46.2)	0.486
Cycle (n, %)			
First	48 (55.8)	17 (65.4)	0.368
Second	38 (44.2)	9 (34.6)	0.422

Difference in the number of days for recovery statistically significant between the two groups.

OHSS, we targeted the high risk group with multimodality approach and brought down the incidence of severe OHSS to 0.095% in all IVF cases performed in the study period (1/1056) and 0.89% in the high risk subjects.

Identifying patients who are at-risk is the most critical step in prevention of OHSS. Predictive factors for OHSS can be primary risk factors, which confer an increased risk of OHSS and secondary risk factors, which become apparent during ovarian stimulation when patients with no known predisposing factors experience an excessive response to treatment.¹⁸ In this study too, we incorporated these risk factors and targeted them to preventive strategy. Anti-Mullerian hormone (AMH) produced by the granulosa cells of primary and preantral follicles has been utilised for its clinical usefulness as a predictor of ovarian response and OHSS in ART cycles.^{19,20} High basal AMH (3.3–6.9 ng/ml) is predictive of OHSS and this has been concluded by various workers including Marca et al, Lee et al and Nardo et al.^{21–23} In the present study too, we found that the mean AMH levels in the high risk group were in the higher range with a mean of 6.5 ng/ml and this was reflected by the increased number of retrieved oocytes in this group as compared to group A with statistical significance. Serum estradiol also used as a marker for OHSS was raised in group B as compared to group A in the present study but was not statistically significant.

Of the various mechanisms implicated for the causation of this complication, the angiogenic molecule, vascular endothelial growth factor plays the most pivotal role in the occurrence of OHSS.²⁴ VEGF stimulates neoangiogenesis and vascular hyper permeability by interacting with its VEGF receptor 2 (VEGFR-2). Thus dopamine agonists which inhibit phosphorylation of the VEGFR-2 reduces the vascular permeability and various presentations of OHSS.^{25,26} In pursuance, cabergoline (Cb2) was extensively studied, and was found to bring about a decrease in the severity or incidence or both of OHSS.^{27,28} Similarly GnRH antagonist was administered in the luteal phase on the hypothesis that GnRH antagonist intervenes in the pathophysiological pathway of OHSS by inducing luteolysis.²⁹ Luteolysis results in the decrease of secreted angiogenic ovarian factors associated with OHSS, thus amplifying OHSS regression.³⁰ The use of calcium gluconate infusion for patients with high-risk factors for OHSS is based on the principle that it initially prevents rennin secretion. Reduced rennin results in decreased angiotensin II synthesis. As a consequence, the stimulatory effect of angiotensin II on VEGF production is ameliorated.³¹ Elective cryopreservation of embryos with subsequent transfer in an unstimulated cycle aims to eliminate further hCG exposure in the active cycle. This prevents late OHSS or exacerbation of the existing early OHSS and also avoids the frustration of cycle cancellation.³²

All the aforementioned modalities have been used in isolation or a combination of few to bring about a decline in the occurrence of OHSS. Lin et al. combined cabergoline and embryo cryopreservation after GnRH agonist triggering in GnRH antagonist protocol to prevent OHSS in high risk subjects and found that no patients developed moderate/severe OHSS.³³ Use of albumin for OHSS prevention has conflicting results with Cochrane database depicting limited evidence of benefit from intra-venous albumin administration for prevention or reduction of severe OHSS. Nevertheless, we

had administered Albumin at the time of oocyte recovery in all the study group patients with no adverse reactions.³⁴

Use of GnRH antagonists in the primary prevention of OHSS for ovarian stimulation instead of GnRH agonists is well established as it drastically reduces its relative risk. GnRH-ant usage once patient has an early onset of OHSS, in the luteal phase as a tertiary preventive measure to bring about rapid regression of the syndrome is being tried as a novel strategy.³⁵ However, only limited data on this new concept is available in literature. Lianas et al. in their study, for the first time suggested that luteal GnRH-ant administered after embryo transfer in patients with established severe early OHSS apart from regression of the complication does not compromise the chance of a successful pregnancy outcome.³⁶ In this work by Lainas, the GnRH antagonist prevented patient hospitalisation in addition to a significant improvement in biochemical parameters.³⁶ However we had used GnRH antagonist from the day of oocyte recovery before the occurrence of OHSS and all the patients were asymptomatic by day 8 post retrieval. This depicts a faster recovery in comparison to the aforementioned study.

The secondary outcome measure to be ascertained was the recovery period of the high risk patients once they were administered the preventive measures. Our subjects recovered entirely on the basis of clinical and ultrasound findings as biochemically and haematologically all of them were normal. The mean recovery period in the group of women with moderate and severe OHSS was 7.9 days which is lesser than mean recovery time of 10 days seen in the retrospective study by Nouri et al.³⁷ The only contradictory observation seen in this study was the mean ovarian enlargement which was found to be more in the mild group as compared to the severe group. No exact definition of recovery exists in literature except the Practice Committee of the American Society for Reproductive Medicine 2008 recommendations which stated that “serial clinical and laboratory evaluations provide the means to recognise evidence of resolution”.³⁸ Data on recovery time from severe OHSS is also wanting in literature presently.

The present study for the first time has used most of the preventive modalities available to combat severe early OHSS with a novel strategy of using GnRH antagonist from the day of retrieval. Out of the 112 high risk women only one had severe OHSS but without any biochemical derangements. There has definitely been a decrease in the incidence of severe OHSS compared to figures reported in literature (0.0895% vs. 2–3%); nevertheless more studies with a larger sample size are required to justify the concomitant administration of multiple drugs.

Conclusion

This study with the usage of multipronged approach in an agonist protocol has been able to decrease severe OHSS in high risk subjects to a great extent but the prospective study design, our specific definition of OHSS recovery and the multipronged treatment modality in terms of financial implications may be considered limitations of our study. In order to have a uniform treatment protocol for all study subjects and have a sound data of high relevance for severe OHSS prevention was our objective

even if it involved usage of multiple interventions. The same management protocol gave consistency to the outcome and removed any biases towards any particular intervention. The long protocol has been the dominating treatment in our institution as large numbers of treatment cycles are being carried out which prevents unscheduled operating days and we wanted to study severe OHSS prevention in long protocol although antagonist protocol with individualised stimulation protocol has become the order of the day. The daily outpatient monitoring may be questioned amounting to a burden on the patients but outpatient monitoring keeps up the morale of the patient vis a vis hospitalisation and reduces the financial costs of hospitalisation.^{39,40} Our study adds to the knowledge that targeting the various pathophysiological pathways at different time frames will bring about the prevention of OHSS but further randomised studies may reveal superiority of one intervention over the other.

Conflicts of interest

The authors have none to declare.

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