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Prevention of Ovarian Hyperstimulation Syndrome in High Risk Patients by Combination of Single Calcium Gluconate Infusion and Cabergolin - A Case Study

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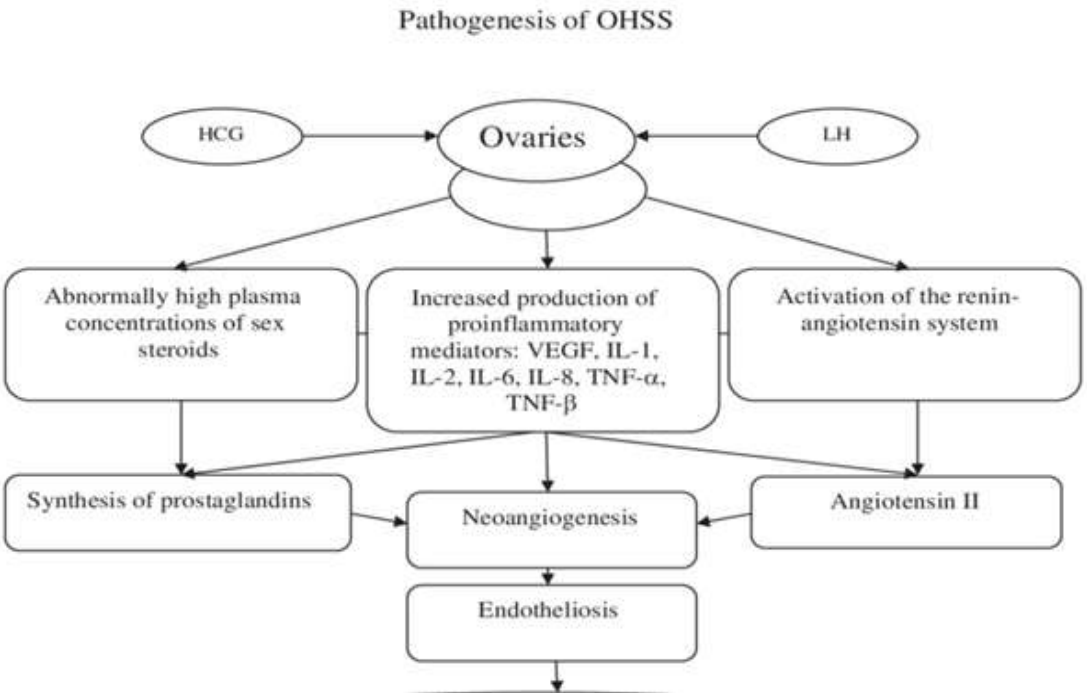
ABSTRACT
Ovarian Hyper stimulation syndrome is a serious iatrogenic complication of ovarian stimulation in IVF cycles. OHSS is associated with exogenous gonadotropin stimulation, followed by hCG trigger for final oocyte maturation. OHSS can be effectively prevented and managed during the early stages. As treatment is mainly empirical, prevention forms the mainstay of management.In this study we have focussed on the combination of a single iv infusion of calcium gluconate, on the day of oocyte retrieval and oral cabergoline therapy for 8 days started on the day of ovulation trigger as a simple outpatient management strategy to prevent OHSS in high risk patients undergoing controlled ovarian stimulation for IVF.

Keywords- OHSS (Ovarian hyper stimulation Syndrome) IVF (in vitro fertilisation)

I. INTRODUCTION

The prevention and treatment of ovarian hyperstimulation syndrome (OHSS), an iatrogenic and potentially life-threatening complication, which may occur in healthy young women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction has been the most dreading and fatal complication of assisted reproductive technology (ART).hCG is thought to be chief mediator of this syndrome which causes increase in mediators as VEGF (Vascular endothelial growth factor) which causes increase in vascular permeability causing the systemic manifestations of OHSS. Second pathophysiological mechanism implicated in OHSS is the intraovarian renin angiotensin system (RAS).The ovarian RAS is involved in regulating vascular permeability, angiogenesis, endothelial proliferation, and prostaglandin release. As hCG causes a strong activation of the RAS, evidenced by high renin activity in the follicular fluid of women with OHSS. Overstimulation of this cascade, togetherwith increasing VEGF levels, is postulated to synergistically potentiate OHSS.



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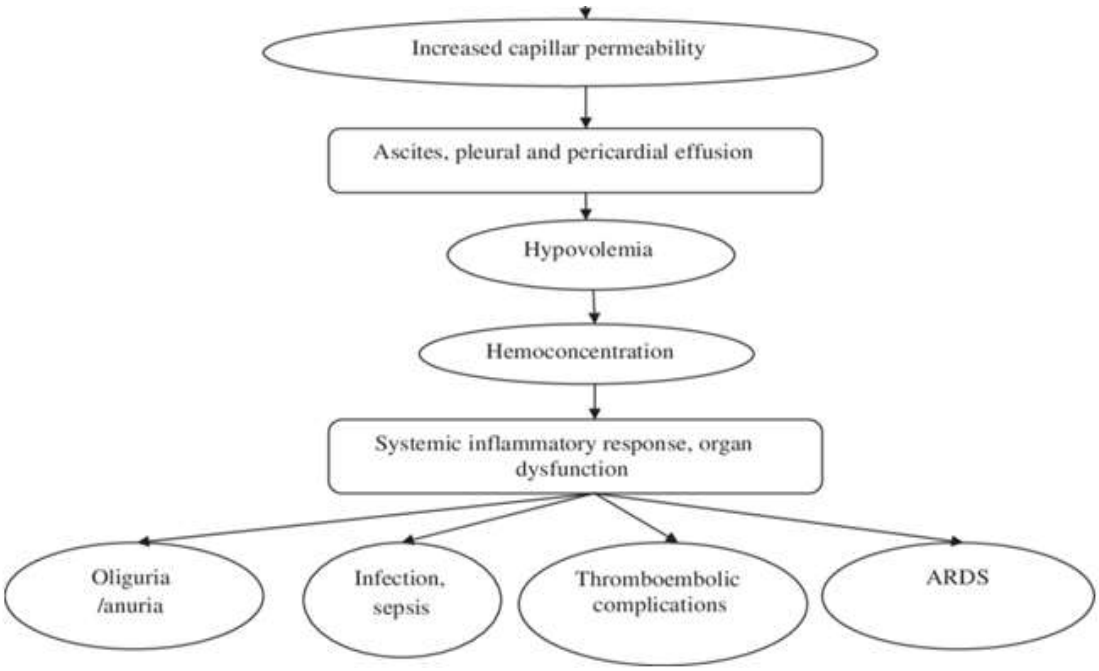

The preventive strategies mainly target to identify the women at high risk of developing OHSS and institution of various pharmacological and non-pharmacological interventions to prevent the same. The pharmacological tools being used are: low-dose follicle stimulating hormone (FSH) or gonadotropin-releasing hormone antagonist protocol during stimulation, albumin infusion at the time of oocyte recovery, dopamine agonist cabergoline (Cb2) started from the day of ovulation trigger and institution of an insulin sensitizer like metformin, whereas the non-pharmacologic modalities incorporated are: Coasting, cycle cancellation, cryopreservation of all embryos for future transfer or use of in vitro maturation.[1,2] Although these preventive measures have not been able to completely eliminate this iatrogenic complication but have definitely brought about a reduction in the severity of OHSS as, it is the, severe OHSS, which is the cause of maximum concern.[3] Severe forms of OHSS may complicate 0.5-5% of in vitro-fertilization (IVF) cycles and can lead to severe morbidity and even mortality if not timely and appropriately intervened.[4] As the search for an ideal preventive therapy continued, a new and innovative therapy in the form of calcium gluconate infusion(4) was introduced in the armamentarium of reproductive specialists to prevent this potentially dreadful complication, however, data and literature on its effectiveness is presently limited.[5,]

In our study, we have shifted our focus on use of Calcium gluconate. a recent innovative therapy for the prevention of OHSS in high risk patients, in addition to use of cabergoline and Cryopreservation of the embryos for the next cycle transfer. We did not cancel the cycle and pickup was done in same cycle. Also Coasting and Albumin infusion was not done in any high risk patient.

STUDY DESIGN

It was a case study in which thirty patients who were at high risk of OHSS based on Basal Antral follicle count and high serum AMH were included, who visited our clinic from Nov 2021 to Jan 2022.

The inclusion criteria or patients who were at high risk for OHSS were, serum AMH >6.00 ng/ml, Antral follicular count of 15 or more and known case of PCOS with age limit 25-35 yrs.

The patients were started on GnRH Antagonist protocol on the day of stimulation, starting with the minimal dose of Gonadotrophins, doses adjusted thereafter as per the ovarian response as evident on the trans vaginal sonography. GnRH agonist trigger (DECAPEPTIDYL) (0.2mg) was administered if greater than three follicles reached a mean diameter of 18 mm. Oocyte retrieval was carried out transvaginally under ultrasound guidance 36 h after hCG administration.

The patients were started on Tab cabergoline 0.5 mg once a day for 8 days starting from the day of ovulation trigger and single calcium gluconate infusion. It was prepared by dissolving 10 ml of 10% calcium gluconate solution in 200 ml of physiologic saline and

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instituted over a period of 40 min. This infusion was administered within 30 min of oocyte retrieval on the day of ovum pickup.

Cycle cancellation was not done and the pickup was done in the same cycle, None of the patient underwent colloid infusion. Cryopreservation of embryos was done and fresh transfer was not done, hence we concentrated on the Early onset OHSS.

Symptoms were monitored and patients were asked to maintain proper hydration and intake output monitoring. All the high risk subjects were managed on an out-patient basis with daily clinical and sonological monitoring and hospitalized only if they went into severe OHSS or their clinical condition mandated close supervision..A baseline hematological and biochemical profile on the day of pick up and daily thereafter was also carried out for the study group subjects as a part of monitoring for OHSS.The classification of OHSS is stated below-

Category features	Features
Mild OHSS	Abdominal bloating
	Mild abdominal pain
	Ovarian size usually <8 cm
Moderate OHSS	Moderate abdominal pain
	Nausea±vomiting
	Ultrasound evidence of ascites
	Ovarian size usually 8–12 cm
Severe OHSS	Clinical ascites (±hydrothorax)
	Oliguria (<300 ml/day or <30 ml/h)
	Hematocrit >0.45
	Hyponatremia (sodium <135 mmol/l)
	Hypo-osmolality (osmolality <282 mOsm/kg)
	Hypoproteinemia (serum albumin <35 g/l)
	Ovarian size usually >12 cm
Critical OHSS	Tense ascites/large hydrothorax
	Hematocrit >0.55
	White cell count >25 000/ml
	Oliguria/anuria
	Thromboembolism
	Acute respiratory distress syndrome

OHSS, ovarian hyperstimulation syndrome.

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II. RESULTS

We used the basal AMH level on the day of stimulation along with the antral follicular count to predict high risk for OHSS.

The number of small antral follicles at the beginning of a cycle is related to age and may reflect the ovarian reserve. Simlar to our study In a study by Kwee et al, an antral follicle count (AFC) >14 had the highest sensitivity (82 %) and specificity (89 %) to positively predict ovarian hyper-response [6]. Basal Anti-Müllerian hormone (AMH) levels prior to COS have also been shown to be predictive for OHSS [7]. Furthermore, AMH predicts ovarian response independently of age and PCOS [7].

In the thirty patients chosen for study, four patients reported mild symptoms of OHSS, including slight abdominal pain and nausea, rest all of patients did not have any symptomatic manifestations of OHSS and the patients were followed daily for symptoms upto 10 days after pickup and adequate hydration was advised. None of the patients in our study required inpatient management or IV colloid infusion. Four incidences of mild OHSS were managed on the outpatient basis. None of the patients developed moderate or severe OHSS,. The patients with mild and moderate OHSS were monitored on an out-patient basis until the resolution of signs and symptoms. None of the patients who were started on calcium gluconate injection developed any allergic reactions, anaphylaxis, symptoms or signs of hypercalcemia, or other side effects.

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AFC	No of patients	AMH range(ng/ml)	OHSS incidence
15-20	8	6-8	none
20-25	11	8-10	One, mild OHSS
>25	13	>10	Three, mild OHSS

III. DISCUSSION

Of the various pathophysiological mechanisms implicated for the causation of OHSS, it is the angiogenic molecule, vascular endothelial growth factor (VEGF), which has been found to be the biggest mediator of this potentially dreadful complication.[8] It has been proven that VEGF stimulates new blood vessel development and vascular hyper permeability by interacting with its VEGF receptor 2 (VEGFR-2). Thus various studies were carried out, which have proven that Dopamine agonists can inhibit phosphorylation of the receptor VEGFR-2 and can thus reduce the vascular permeability and various presentations of OHSS in the ART cycles.[9] In pursuance, Cb2 was therefore extensively studied and was found to bring about a decrease in the severity or incidence or both of OHSS.[10]

S.no	Summary statement	Grade of Recommendation
1.	There is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduces the incidence of OHSS	Grade A
2.	There is fair evidence that calcium lowers OHSS risk.	Grade B
3	There is fair evidence that cryopreservation prevents OHSS, based on the results of two small RCTs.	Grade B
4	There is good evidence to recommend the use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval in order to reduce the risk of OHSS	Grade A
5	Women with PCOS, elevated AMH values, and elevated AFC may benefit from ovarian stimulation protocols that reduce the risk of OHSS	Grade B
6	There is insufficient evidence to conclusively state that albumin lowers OHSS risk.	Grade C

Another observation found in a separate study was the stimulatory role of low intracellular calcium on adenylyl cyclase, which resulted in cyclic adenosine monophosphate (cAMP) synthesis and thus, renin release.[11] Thus it was inferred that although calcium does not directly control renin secretion, increased calcium inhibits and decreased calcium amplifies cAMP-stimulated renin secretion.Gurgan et al. (12) in their retrospective study also researched and found that calcium infusion successfully prevents the development of severe OHSS and significantly decreases OHSS occurrence rates without any major adverse effect when used for high-risk patients such as those with polycystic ovary syndrome (PCOS). Both Cabergolin and calcium are useful for the prevention of this iatrogenic complication,.

The most critical step in the prevention of OHSS is the identification of the women at high risk as it guides a clinician to make changes to the ovarian stimulation regimen and to add other preventative measures. Predictive factors for OHSS can be primary risk factors, which confer an increased risk of OHSS on patients and secondary risk factors, which become apparent during ovarian stimulation when patients with no known predisposing factors experience an excessive response to treatment. In this study too, we considered these risk factors and targeted them to predict the ovarian hyper response. Antral Follicular count and serum AMH both are good predictors of ovarian hyper response as one mild OHSS case was reported in AMH in range of (8-10 ng/ml) with AFC (20-25) and three cases of mild OHSS in AMH range greater than 10 ng/ml and AFC greater than 25.

In this study we used the two drugs, We combined tab cabergoline for 8 days and the single infusion of Calcium gluconate on the day of ovum pickup, instead of a conventional three days which reduced the number of visits of patient and monitored them by adequate input output monitoring by thirst and urine output and advised

the patients to maintain hydration.Both drugs ultimately targeted the same key molecule: VEGF. The pathway of reaching the target and the mode of administration of both the drugs might be different but the preventive mechanism was same, i.e., either antagonizing VEGF receptor as in Cabergolin or decrease VEGF levels as with calcium gluconate infusion.Our observations in this present study was only limited to the occurrence of early onset of as we carried out freezing of all the embryos so late onset of OHSS was not evaluated.

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IV. CONCLUSION

We can say that the combination of Cabergolin and single dose calcium gluconate infusion were found to be effective for the prevention of OHSS and most importantly in decreasing the severity of this potentially life-threatening complication of ART.Anyeffect on the implantation process and the comparison of the pregnancy rate, implantation rate and miscarriage rate was not computed which accounts for the limitation of this study. Larger well designed trials need to be carried out incorporating the aforementioned factors as well as measurements of VEGF levels in both the study groups.Both drugs are safe, cheap and have are successful in preventing OHSS.Cabergolin and single dose calcium gluconate infusioncan be employed as a treatment strategy for patients with high risk factors for OHSS undergoing ART cycles in a more patient friendly way as it reduces the number of clinical visits and even high risk women can be easily managed on an outpatient basis.

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