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Switch Off; A Safety Measure Against Unexpected OHSS

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Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic adverse effect of ovarian stimulation in susceptible women. It is an exaggerated response to ovarian stimulation characterized by the shift of fluid from the intravascular space to the third space, specifically the abdominal cavity. OHSS is associated with physical and psychosocial morbidity and may lead to maternal death.
Exposure of the stimulated ovaries to HCG leads to the production of vascular endothelial growth factor (VEGF) which is involved in the initiation of the OHSS. The VEGF-induced vascular permeability leads to loss of fluid into the third space (ascites or, less commonly, pleural, and pericardial effusions). In severe OHSS cases hypovolemia, with a typical loss of 20% of blood volume may occur.

Case presentation: 54 cases, all of them were complaining of primary infertility. All patients were average responders, ICSI was planned for all of them. They were stimulated with gonadotropin in a long agonist protocol and triggered by 5000 HCG followed by ovum pickup under transvaginal sonographic guide then Treatment by letrozole immediately after oocyte retrieval and for 5 days plus agonist continued for 5 days plus LPS FOR.

Conclusion: The concomitant use of Letrozole after OR with agonist may be considered for "switching off" unexpected hyper response, to protect them from OHSS.

Keywords: OHSS, switch off, prevention.

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Case Series

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic adverse effect of ovarian stimulation in susceptible women. It is an exaggerated response to ovarian stimulation characterized by the shift of fluid from the intravascular space to the third space, specifically the abdominal cavity. OHSS is associated with physical and psychosocial morbidity and may lead to maternal death(1).
Human chorionic gonadotrophin (HCG) administration after controlled ovarian stimulation by gonadotropins underlies most cases of OHSS. Exposure of the stimulated ovaries to HCG leads to the production of vascular endothelial growth factor (VEGF), which is involved in initiating the OHSS (1).

In the susceptible patient, human Chorionic Gonadotropin (hCG) administration, in the presence of high estradiol concentration, leads to overexpression of vascular endothelial growth factor (VEGF) in the ovary (2). In granulosa cells of stimulated ovaries, the expression of vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR-2) peak 48 hours after hCG injection (3). VEGF acts on adhesion molecules such as VE-cadherin, resulting in the loosening of endothelial intercellular junctions(3). Co-administration of a dopamine agonist inhibits phosphorylation of the receptor VEGFR-2 (4).

The VEGF-induced vascular permeability leads to loss of fluid into the third space (ascites or, less commonly, pleural and pericardial effusions). In severe OHSS cases, hypovolemia, with a typical loss of 20% of blood volume, may occur (5).

Many risk factors increase OHSS incidence: a previous history of OHSS, PCOS, increased antral follicle count (AFC), or high levels of anti-Müllerian hormone (AMH). Mild forms of OHSS are common and affect up to 33% of IVF cycles, but moderate and severe forms of OHSS complicate 3-8% of cycles (6).

Ovarian hyperstimulation syndrome can be classified clinically as early and late according to the time of onset. Early OHSS occurs within 10 days after the HCG administration. Late OHSS presenting 10 days or more after HCG administration indicates endogenous hCG stimulation from early pregnancy (7).

The classification of OHSS severity proposed according to the RCOG guideline may be mild, moderate, severe, and critical (8). The long agonist protocol could be used more than the antagonist protocol in average responders.
There are many stages to prevent OHSS as the treatment protocol (9), choice of trigger (10), elective cryopreservation of oocytes/embryos, mild stimulation/ individualized FSH dose, co-treatment with metformin, dopamine agonist, coasting, and cycle cancellation.

In the current case series, a long agonist protocol was used in average responders, as Lambalk et al. 2017 suggested “Switching off” the cycle in unexpected hyperresponders was performed by simultaneously administering aromatase inhibitor and GnRH agonist. Letrozole should decrease estradiol by blocking ovarian aromatase, and the agonist will prevent pituitary stimulation from low E2, which may result in ovarian stimulation with subsequent rise of E2 and VEGF production (11).
Case series have an important role in the progress of medical science. They allow the discovery of unexpected effects (adverse or beneficial) and the mechanisms of drugs, and they play an important role in medical education. Case series are one of the cornerstones of medical progress; they introduce many new ideas in medicine.

Case Series Presentation

We present 54 cases, all of them were complaining of primary infertility. All patients were average responders with AMH <5 and AFC <20; ICSI was planned for all of them. They were stimulated with 150-225 IU gonadotropin in a long agonist protocol and triggered by 5000 HCG followed by ovum pickup after 36 hours under transvaginal sonographic guide, then Treatment by letrozole 5 mg immediately after oocyte retrieval and for 5 days plus agonist continued for 5 days plus LPS FOR. Freeze all was done. Estradiol was measured at hCG and 5 days after OR. An unexpectedly high response was defined as a

multifollicular response with > 15 oocytes retrieved.

Discussion

We present 54 cases of ICSI cycles, all of them were liable to OHSS as the number of COCs was (22.85 ± 5.33), table 1 mature oocytes (18.80 ± 5.47) fertilization rate (15.22 ± 5.10), number of top quality embryos (10.54 ± 4.24). These cases were managed successfully with letrozole 5 mg immediately after oocyte retrieval and for 5 days plus agonist continued for 5 days plus LPS FOR to prevent the occurrence of OHSS.

Table 1: Embryological outcomes

	No. (54)	%
Total COCs	22.85 ± 5.33	22.0 (15.0-40.0)
Total M2	18.80 ± 5.47	18.0 (9.0-36.0)
Total fertilized oocyte	15.22 ± 5.10	15.0 (8.0-30.0)
Total number OF embryos	14.24 ± 5.16	13.0 (5.0-29.0)
Number of top quality embryos	10.54 ± 4.24	9.0 (4.0-24.0)

Aromatase inhibitor usage leads to Estradiol decrease, which would induce Granulosa cell apoptosis, Decrease receptors for hCG/LH, Decrease VEGF secretion, and Decrease vascular permeability (12).

No cases of severe OHSS were observed in the current series, with no effect on the cumulative pregnancy rate (66.7%) (Table 2).
Estradiol measurement before OR and after treatment with this protocol shows a sharp decline in the E2 level with (p<.001) (Figure 1 and Table 3).

Table 2: Pregnancy rate

Pregnancy rate	No. (54)	%
Positive	36	66.7%
Negative	18	33.3%

Previous studies reported that GnRH antagonist administration in the luteal phase improved severe OHSS, decreasing the ovarian volume, estradiol, and progesterone concentrations (13-14). Similar findings were observed in previous studies with aromatase inhibitors, as in a randomized controlled trial conducted in 2008 To investigate the effect of letrozole—an oral aromatase inhibitor—on E2, P, and LH levels when administered during the luteal phase after oocyte retrieval in IVF/intracytoplasmic sperm injection (ICSI) cycles. The administration of 2.5 mg of letrozole during the luteal phase has an impact on corpus luteum (CL) function. It reduces serum E2 levels, allowing a faster LH concentration recovery. This may be of interest not only for egg donors but also in patients at high risk of ovarian hyperstimulation syndrome (OHSS) who freeze all their embryos or who cancel hCG administration to reduce the potential risk that high E2 levels pose (15).
Another RCT done by Rana Afzal Choudhary et al. 2021 In this prospective single-centred, randomized, parallel-arm study, 122 patients were randomized to receive oral letrozole (n=61, 2.5 mg twice daily) or ganirelix acetate (n=61, 0.25 mg subcutaneously daily) from the day of egg retrieval for the next seven days. They concluded that letrozole and ganirelix acetate have the same efficiency for the overall prevention of OHSS, whereas letrozole was more effective in preventing moderate OHSS. Letrozole had better patient satisfaction and was cheaper compared to GnRH antagonists (16).

Other studies that differ from our study as Ya-Qin Wang et al. 2015 study that uses letrozole, mifepristone, cetrotide, and three-drug combinations during the luteal phase after oocyte retrieval for prevention of severe ovarian hyperstimulation syndrome (OHSS) in high-risk patients but in this study the incidence of severe OHSS, the paracentesis rate, the duration of hospitalization and the days of luteal phase in each subgroup of treatment groups was not significantly decreased despite of the decrease of serum estradiol levels in the letrozole and three-drug combination therapy group (17).

Table 3: **E2 level before and after the intervention of switch off**

E2	Before treatment (n= 54)	After treatment (n= 54)	P-value
Mean ± SD	3911.54 ± 3652.57	573.06 ± 501.53	<0.001*
Median (Range)	2595.5 (962.0-21284.0)	481.0 (21.0-2780.0)	

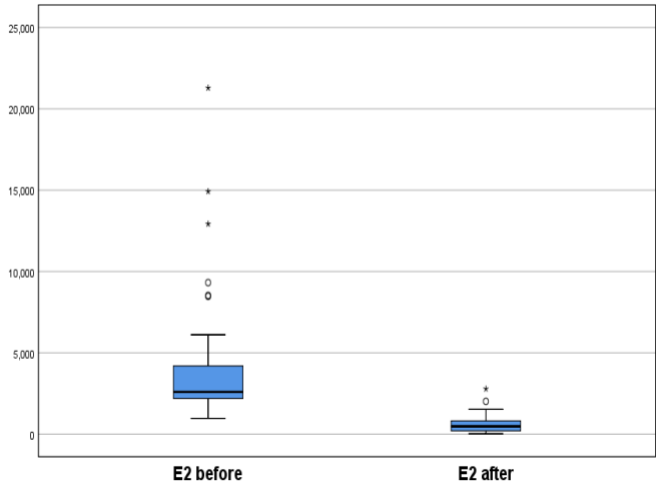

Figure 1. **E2 level before and after the intervention of switch off**

Another study was a systematic umbrella review in 2023 concluded that Letrozole did not prevent moderate-to-severe OHSS (18).

It has to be noted that the indication and timing of the switch-off are important. In the present study, we used average responder cycles, which unexpectedly resulted in hyperresponse and not high-risk patients. Moreover, a switch-off was initiated before any occurrence of actual OHSS.

Limitations

This study is limited by its relatively small sample size and the nature of the study design.

Conclusion

In conclusion, the concomitant use of Letrozole after OR with agonist may be considered for "switching off" unexpected hyper response to avoid life-threatening severe OHSS.

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