

Case Report

# Letrozole and Cabergoline Co-administration in the Early Luteal Phase for Prevention of OHSS in a High Risk Patient Undergoing Ovarian Stimulation for IVF

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## Abstract

**Background:** In the face of a high risk for OHSS situation, many strategies have been suggested to prevent it; however, none of the proposed strategies completely prevents OHSS. We report a case of a successful IVF pregnancy and complete prevention of OHSS in a patient at high risk of developing OHSS by co-administration of a dopamine agonist and an aromatase inhibitor during the early luteal phase of the cycle.

**Case:** A 21-year-old patient with primary infertility, secondary to severe oligoasthenospermia of the male partner was stimulated with rec-FSH/GnRH antagonist protocol.

Final oocyte maturation was achieved by administration of 5000 IU of HCG. Due to the high risk of OHSS, patient received directly post oocyte retrieval up to the day of embryo transfer, daily 5 mg Letrozole and 0.5 mg Cabergoline. One embryo was transferred on day 5 post oocyte retrieval. The patient did not develop any early nor late OHSS while a successful ongoing pregnancy was achieved.

**Conclusion:** Our findings suggest that the use of cabergoline and letrozole in the early luteal phase for the prevention of OHSS, in patients triggered with hCG, might be a potential new strategy. However their use and effect should be further investigated in prospective randomized studies.

**Keywords:** IVF (In Vitro Fertilization); OHSS (Ovarian Hyperstimulation Syndrome); Letrozole; Cabergoline

## Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic and potentially fatal complication resulting from excessive ovarian stimulation. Reported incidence varies from 1% to 14% of all IVF/ICSI cycles [1]. The severe form that leads to hospitalization occur in 0.1-3%, however, moderate cases of OHSS of all cycles is estimated to be between 3-6% [2,3].

In the face of a high risk for OHSS situation, in long agonist protocols many strategies have been suggested to prevent OHSS, although still performing a fresh embryo transfer, as coasting [4,5], albumin administration [6], or in vitro oocyte maturation [7]. However, none of the proposed strategies completely prevents OHSS. On the other hand in antagonist protocols the use of GnRH agonists to trigger final oocyte maturation [8] eliminates OHSS to almost extremely rare late event and it is up to the physician to decide either to vitrify all embryos or to transfer a single fresh embryo with intense luteal support.

Recently, dopamine agonists were proposed as a prophylactic treatment for OHSS in women at high risk. It was demonstrated that cabergoline inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability without affecting luteal angiogenesis [9]. However, recent randomized [10,11] and non randomized studies [12] indicate that, the prophylactic luteal treatment with the dopamine agonist, cabergoline reduces the incidence of both moderate and severe OHSS, in high risk patients undergoing IVF.

On the other hand, since serum estradiol concentrations on the day of hCG administration seem also to play a role in OHSS development [13], and letrozole is able to inhibit the conversion of androgens into

estrogens [14]. One possible way of preventing early OHSS would be the suppression of production of estrogen during the early luteal phase by reducing the secretive capacity of the sustained corpora lutea. Therefore, the administration of aromatase inhibitor letrozole during the luteal phase in IVF cycles might offer another treatment modality for patients at high risk for OHSS. The two existing clinical trials [15,16], both of them performed with oocyte donors, confirmed that letrozole reduces the luteal E2 levels in stimulated cycles.

Based on our knowledge, no data exist regarding the combination of these two treatments, dopamine agonist and aromatase inhibitor as OHSS prevention method in IVF stimulated cycles. We report a case of successful pregnancy and completely prevention of OHSS in a patient at high risk of OHSS by using the above combination treatment during the luteal phase of the cycle.

## Case Report

A 21-year-old gravida zero and her partner presented with primary

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infertility secondary to severe oligoasthenospermia due to translocation 46XY t(7q/11q) (7p/11p).

The couple had undergone an IVF/ICSI cycle with PGD without an embryo transfer due to lack of genetically normal embryos. For her second trial, the patient was stimulated with a rec-FSH (200 IU)/ GnRH antagonist protocol.

On day 7 of stimulation the dose of rec-FSH was decreased to 150 IU due to the risk of OHSS. On Day 9 of stimulation, an E<sub>2</sub> level of 5000 pg/ml was measured and 50 follicles were visualized. The physician on duty had limited experience with a GnRH agonist trigger to avoid OHSS and therefore final oocyte maturation was achieved by administration of 5000 IU of HCG.

52 oocytes were retrieved, with 38 Metaphase II oocytes. 23 oocytes were fertilized with ICSI, and on day three 13 embryos were biopsied for PGD. There was one genetically normal embryo that was transferred on day 5 post oocyte retrieval. Due to the risk of OHSS, patient was advised to follow a protein rich diet and directly post oocyte retrieval up to the day of embryo transfer, 5 mg letrozole daily (2x2.5 mg, Femara®) and 0.5 mg cabergoline (Dostinex®) were administered orally. The patient's status was evaluated on day one post retrieval and on the day of ET (Day 5). The patient did not develop any signs of OHSS. On day 5 post oocyte retrieval, one genetically normal embryo was transferred and at 7 of gestation, a viable singleton pregnancy could be visualized on ultrasound. The patients did not develop any early nor late OHSS.

## Discussion

The current case report indicates a potential new strategy for dealing with prevention of early and late OHSS, especially in cases where the long agonist protocol is utilized, as well as in cases with antagonist protocol triggered with hCG instead of agonist due to limited experience on that new technique.

Recently, dopamine agonists were proposed as a prophylactic treatment for OHSS in women at high risk. It was demonstrated that cabergoline inhibits partially the VEGF receptor 2 phosphorylation levels and associated vascular permeability without affecting luteal angiogenesis.

On the other hand, since serum estradiol concentrations on the day of hCG administration seem also to play a role in OHSS development and letrozole is able to inhibit the conversion of androgens into estrogens [1]. One possible way of preventing early OHSS would be the suppression of production of estrogen during the early luteal phase by reducing the secretive capacity of the sustained corpora lutea. Therefore, the administration of aromatase inhibitor during the luteal phase in IVF cycles might offer another treatment modality for patients at high risk for OHSS [2,3].

One can argue why to risk performing ET in a very high OHSS risk patient instead of total freezing of the produced embryo. We agree with that concept, however, still patients exist, who interpret no transfer as a failure. On the other hand, in this particular patient described above, the embryos were biopsied for PGD and only one genetically normal embryo was diagnosed.

The medical management of the luteal phase herein described, presents an alternative for high OHSS risk patients triggered with hCG

for final oocyte maturation, still undergoing fresh embryo transfer. The cautious use of such agents as cabergoline and letrozole within the implantation window appears as a safe approach instead to total freezing in patients willing to undergo embryo transfer or for patients misjudged as moderate risk for OHSS and still at risk to develop OHSS. Especially in long agonist protocol where the risk of OHSS is impossible to be eradicated, the current concomitant use of the above medications should be further analyzed.

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