

# First Case of Severe Late Ovarian Hyperstimulation Syndrome in a Patient who was Treated with In-Vitro Maturation of Human Oocytes and Planned Short Gonadotropin Stimulation

Ayşe Seyhan, MD; Baris Ata, MD; Seang Lin Tan, MD, MBA; Weon Young Son, PhD; Michael H Dahan, MD\*

\*Michael H Dahan, MD

Department of Obstetrics and Gynecology, McGill University, Canada.

Tel: 1-514-843-1650; Fax: 1-514-843-1496; Email: dahanhaim@hotmail.com

## Abstract

In-vitro maturation is a technique used to perform assisted reproduction in women with high ovarian reserve, who are at risk for ovarian stimulation. With this technique occasionally 3-4 days of gonadotropins are planned to enlarge the follicles and aid in oocyte collection. Human chorionic gonadotropin is also given to ease the collection. These few days of ovarian stimulation were felt to be insufficient to cause severe ovarian hyperstimulation syndrome. However, the case of a 32 year old women with polycystic ovary syndrome who underwent planned ovarian stimulation with four days of gonadotropins for a stimulated IVM cycle, and who developed severe ovarian hyperstimulation syndrome is presented. This is the first case of ovarian hyperstimulation syndrome in an IVM cycle. Clearly, only unstimulated IVM can be used to completely avoid ovarian hyperstimulation syndrome.

## Keywords

Ovarian hyperstimulation syndrome; IVM; In-vitro maturation; OHSS

## Background

Ovarian hyperstimulation syndrome (OHSS) is the most significant and potentially lethal complication of controlled ovarian stimulation (COS) in IVF cycles. Preventive measures against OHSS in at risk patients have been developed including in vitro maturation of human oocytes (IVM). IVM has the advantages of reducing or eliminating the use of gonadotropins, therefore it plays an important role for patients who are at high risk of OHSS. Currently, there were no cases in the medical literature of OHSS recorded in patients who underwent IVM.

It was demonstrated that a short course of gonadotropins will stimulate the growth of follicles as well as thicken the endometrium in IVM cycles [1]. Patients who received short courses of gonadotropins for IVM also have more MII oocytes collected when compared to patients who only received estrogen supplementation, both of which are used to develop a receptive endometrium [1]. Slightly larger follicles, which occur when a few days of gonadotropins are used as stimulation, are easier to collect. Irrelevant of whether a short course of gonadotropins is prescribed the HCG trigger is given when the lead follicle is 10 to 12 mm in diameter. This practice is based on a study which demonstrated higher

implantation and clinical pregnancy rates when the leading follicle was 12 mm at the day of HCG administration as opposed to lead follicles of 14mm or greater or smaller than 10 mm in diameter [2]. At our institution, priming with 10 000 IU hCG followed by oocyte collection 38-hours later is the standard protocol in IVM cycles [3]. The planned use of three to five days of gonadotropins started cycle day 2 to 3 in IVM cycles has become common. This is termed short stimulation IVF- IVM and permits the benefits listed previously in this article, including triggering at a 12mm diameter lead follicle. Prior studies of IVM have demonstrated total elimination of severe OHSS. Herein, we report the first case in the medical literature, of severe late OHSS who presented with hemoconcentration, ascites and decreased serum albumin levels despite undergoing IVM with planned short stimulation. It was previously believed those 3 to 5 days of gonadotropins and follicles  $\leq 12$ mm diameter would not lead to OHSS.

## Case Presentation

A 32 year- old woman with polycystic ovary syndrome presented to our clinic with 13 years of primary infertility, oligomenorrhea with cycles 45 to 90 days, and a polycystic ovary on ultrasound. She underwent right salpingo-oophorectomy due to ovarian torsion 2004. Three years prior to presentation a laparoscopy for dysmenorrhea revealed extensive pelvic adhesions and tubal blockage. She was taking 850 mg metformin twice daily.

Due to tubal factor and PCOS, she underwent a short stimulation IVM protocol. She was stimulated for 3 days with 225 IU and 1 day with 300 IU recombinant follicle stimulation hormone- alpha. This dose was selected due to the previous unilateral oophorectomy and a BMI of 26 kg/m<sup>2</sup>. Injections were started on the third day of a progesterone withdrawal bleed. However, few eggs were collected and few matured. A chemical pregnancy occurred.

A second fresh short stimulation IVM protocol was planned with 300 IU/day of gonadotropins for 5 days starting from day 3 of a progesterone induced withdrawal bleeding. The increased dose was chosen to increase follicle diameter and hopefully increase the number of eggs and MII oocytes collected. On day 8 of cycle, the US revealed the presence of 1 follicle measuring 12 mm, 10 follicles measuring 10 mm, 9 follicles measuring 8 mm and the serum estradiol level was 6013 pmol/l. The patient was triggered with 10000 hCG that evening followed by oocyte retrieval 38-hours later. Vaginal progesterone was started on the day of oocyte collection. Thirty- seven oocytes were collected, 33 of which were mature or matured and led to 27 embryos. Thirteen blastocysts were obtained. One blastocyst was transferred and 12 were cryopreserved.

Sixteen days after oocyte collection, she developed abdominal distension, vomiting, pain, shortness of breath and subjectively reduced urinary output. The serum beta- hCG level was 225 IU/L. Her hematocrit was 42%, her leukocyte count (WBC) was 19,460 X 10<sup>6</sup>/ml, hepatic and renal function tests were normal, while her serum albumin level was 28 g/dl. An ultrasound exam revealed free fluid in the pouch of Douglas. She was admitted with the diagnosis of severe OHSS.

The patient was managed with intravenous crystalloid infusion, 25% albumin supplementation and thromboembolic prophylaxis. On day 18 and 20 after oocyte collection, 1 and 2 liters of clear ascites was drained by transvaginal puncture. The patient was discharged 7 days after admission. The patient had a spontaneous miscarriage at 5 weeks of gestation.

## Discussion/Conclusion

There are two distinct patterns of OHSS according to the onset of symptoms: early-onset OHSS occurs 3-7 days after HCG administration and late onset OHSS occurs at least 12 days after hCG administration. hCG and the presence of ovarian tissue are mandatory for the development of OHSS. Early OHSS is a consequence of exogenous hCG whereas late onset OHSS is induced by endogenous hCG produced from implanted trophoblast cells of a pregnancy. Although the source of hCG is different, the main determinant of OHSS depends on the concentration of vasoactive substances produced by hyperstimulated ovaries in response to hCG. This is reached earlier in early onset OHSS cases with the bolus injection of hCG. In the later type sustained hcg activity increases progressively following pregnancy implantation. In both types of OHSS hCG triggers granulosa cells to produce vasoactive substances. Women who become pregnant following oocyte donation don't develop OHSS. Another important contributor to the development of OHSS is the use of gonadotropins for ovarian stimulation. Hyperphysiologic gonadotropins whether exogenous or from a pituitary adenoma are needed for OHSS to develop [4]. These gonadotropins increase the number of follicles that continue development.

In-vivo matured oocytes are often collected from small follicles at the time of retrieval in IVM cycles [5]. Immunohistochemical studies in granulosa cells detected LH binding sites (LH-R) in follicles at least 9.5 mm in diameter. It is likely that these follicles therefore, have the potential to respond external HCG administration. Multiple follicles even though of a smaller diameter seem to have the capacity to produce vasoactive substances and develop OHSS. Although, the vasoactive substances produced per follicle should be many magnitude lower than those from larger diameter follicles due to the radically decreased volume of accessory cells. These cells are greatly reduced in smaller follicles since they are a function of the radius of the follicle squared. (Surface Area of a Sphere =  $4 \pi r^2$ ). This case demonstrates that when the number of follicles which develop is large, even though of extremely small diameter, and gonadotropins are used for as few as 5 days, OHSS can develop even with IVM. This is the first case of OHSS at IVM and was likely caused by the use of gonadotropins. It suggests that even though a rare complication in these cases, 3 to 5 days of gonadotropin stimulation should be avoided and unstimulated IVM preferred in high risk patients.

## References

1. Elizur SE, Son WY, Yap R, Gidoni Y, Levin D, Demirtas E, Tan SL 2009. Comparison of low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation in in-vitro maturation cycles with thin endometrial lining. *Fertil Steril.* 2009;92:907-12.
2. Son WY, Chung JT, Herrero B, Dean N, Demirtas E, Holzer H, Elizur S, Chian RC, Tan SL. Selection of the optimal day for oocyte retrieval based on the diameter of the dominant follicle in hCG-primed in vitro maturation cycles. *Hum Reprod.* 2008; 23:2680-5.
3. Son WY, Chung JT, Chian RC, Herrero B, Demirtas E, Elizur S, Gidoni Y, Sylvestre C, Dean N, Tan SL.. A 38 h interval between hCG priming and oocyte retrieval increases in vivo and in vitro oocyte maturation rate in programmed IVM cycles. *Hum Reprod.* 2008; 23:2010-6.
4. Djerassi A, Coutifaris C, West VA, Asa SL, Kapoor SC, Pavlou SN, Snyder PJ. Gonadotroph adenoma in a premenopausal woman secreting follicle-stimulating hormone and causing ovarian hyperstimulation. *J Clin Endocrinol Metab.* 1995; 80:591-4.

5. Son WY, Chung JT, Demirtas E, Holzer H, Sylvestre C, Buckett W, Chian RC, Tan SL. Comparison of in-vitro maturation cycles with and without in-vivo matured oocytes retrieved. *Reprod Biomed Online*. 2008; 17:59-67.

**Manuscript Information:** Received: September 03, 2015; Accepted: January 18, 2016; Published: January 20, 2016

**Authors Information:** Ayse Seyhan, MD; Baris Ata, MD; Seang Lin Tan, MD, MBA; Weon Young Son, PhD; Michael H.Dahan, MD\*  
Department of Obstetrics and Gynecology, McGill University, Canada

**Citation:** Seyhan A, Ata B, Tan SL, Son WY, Dahan MH. First case of severe late ovarian hyperstimulation syndrome in a patient who was treated with in-vitro maturation of human oocytes and planed short gonadotropin stimulation. *Open J Clin Med Case Rep*. 2016; 1066

**Copy right Statement:** Content published in the journal follows Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>). © Dahan MH 2016

**Journal:** Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.

Visit the journal website at [www.jclinmedcasereports.com](http://www.jclinmedcasereports.com)

For reprints & other information, contact editorial office at [info@jclinmedcasereports.com](mailto:info@jclinmedcasereports.com)