

# Severe Ovarian Hyperstimulation Syndrome despite low dose stimulation in Polycystic Ovarian Syndrome



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## ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of assisted reproduction technology. There is cystic enlargement of the ovaries along with fluid shift from the intravascular compartment to the third space due to increased capillary permeability and ovarian neoangiogenesis. Severe OHSS is uncommon and the condition can be fatal. Low-dose gonadotropin protocols have been introduced to reduce the risk of OHSS in patients with polycystic ovary syndrome (PCOS). The patient being reported had PCOS and developed severe OHSS despite low dose gonadotropin stimulation; which is a rare scenario.

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## INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication which occurs almost exclusively in assisted reproduction technology. It is seen in ovarian stimulation with gonadotropins and clomiphene citrate. The condition is characterized by cystic enlargement of the ovaries and an increase in vascular permeability resulting in a fluid shift from the intravascular to the third space compartments and ovarian neoangiogenesis.<sup>1</sup> The incidence of OHSS is about 5% in women undergoing in-vitro fertilization or intrauterine insemination procedures.<sup>2</sup> The first fatal cases were reported in 1951.<sup>3</sup> The patient being reported developed severe OHSS despite low dose gonadotropin stimulation.

## CASE DESCRIPTION

A 30 year old female, nursing staff (P<sub>0</sub>L<sub>0</sub>A<sub>1</sub>) working abroad, presented with complaints of dyspnoea (mainly on lying down), nausea, abdominal and back pain, and bloating sensation with abdominal distension since 1 week.

She has been married for 7 years. About 2 years ago, she had taken infertility treatment (hysterolaparoscopy with ovarian drilling) and conceived spontaneously, but the pregnancy got aborted in the 1<sup>st</sup> trimester. Currently, she underwent ovulation induction with recombinant- FSH (follitropin alfa 75 IU subcutaneous once daily) for 7 days from day 10 to day 16 of her menstrual cycle. The size of the dominant follicle on the 14<sup>th</sup> and 16<sup>th</sup> day was 15 mm and 18 mm respectively. There were 3 other follicles of size more than 16 mm, and 6 follicles of 13 to 15 mm. Ovulation trigger was given on day 16 with 5000 IU of hCG and intrauterine insemination was done on day 18 of her menstrual cycle. She presented about 2 weeks later with the above mentioned complaints.

On examination, she was conscious, oriented, afebrile and dyspnoeic. Her pulse rate was 100/minute (regular), blood pressure 90/60 mmHg, respiratory rate 28/minute with saturation 92% in room air. She had a body mass index (BMI) of 19.2 kg/m<sup>2</sup>. Mild pitting pedal oedema was present. She had decreased breath sounds in bilateral lung fields. Her abdomen was distended, and fluid thrill and shifting dullness were present.

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Her blood investigations showed leucocytosis (14700 cells/cumm with 80% neutrophils and 20% lymphocytes). Serum albumin was 1.8 mg/dL. Other investigations like renal and liver functions, TSH, electrolytes and urine routine were normal.  $\beta$ -hCG levels were 134 mIU/ml. Ultrasound scan of the abdomen revealed bilateral bulky ovaries with multiple cysts and moderate ascites, and of the thorax showed bilateral minimal pleural effusion. Electrocardiography and echocardiography were normal.

She was started on continuous intravenous fluids (normal saline and ringer lactate at 100 to 150 ml/hour) along with 20% albumin infusions and subcutaneous enoxaparin (40 mg once daily). By day 3 of admission her symptoms started worsening. Repeat ultrasound thorax showed an increase in pleural effusion (right > left).  $\beta$ -hCG levels rose to 1248 mIU/ml suggestive of pregnancy. She had adequate urine output. Her medications were continued the same way with addition of furosemide (20 mg once daily). By day 6 there was symptomatic improvement. She was able to tolerate oral diet without nausea and abdominal bloating. Serum albumin rose to 3.4 mg/dL. Her repeat ultrasound abdomen showed hyperstimulated ovaries being replaced by multiple theca lutein cysts of varying dimensions and minimal ascites. Her pleural effusion also showed regression. She was discharged on day 10 of admission on high protein diet. She was also advised to continue subcutaneous enoxaparin (40 mg once daily) till the 12<sup>th</sup> week of pregnancy. On follow-up after 4 days, she was asymptomatic and her ultrasound thorax showed minimal bilateral pleural effusion.

## DISCUSSION

As mentioned earlier, OHSS is an iatrogenic complication which can be life threatening. The symptoms can get even worse and persist longer if pregnancy is successful. The underlying mechanisms responsible for the clinical manifestations are ovarian cystic enlargement and increase in capillary permeability of mesothelial surfaces, thereby leading to shift of fluid from the intravascular to the third space compartment. Though  $\beta$ -hCG and its analogues, estrogen, estradiol, histamine, prolactin and prostaglandins have all been implicated in OHSS, it is now believed that the increased vascular permeability is due to vasoactive substances such as interleukins, TNF- $\alpha$ , endothelin-1, and vascular endothelial growth factor (VEGF) secreted by the ovaries. This can lead to the development of ascites, pleural effusion, pericardial effusion and edema. The symptoms like abdominal pain, nausea and vomiting are due to ovarian enlargement. There is an increased risk developing deep venous thrombosis and pulmonary embolism due to the hypercoagulable state resulting from hemoconcentration

and hypovolemia. Electrolyte imbalance and acute kidney injury are other noted complications.<sup>1,4</sup>

OHSS is extremely rare without hCG administration, and is believed to be mediated via the production of VEGF, a heparin-binding glycoprotein with vascular permeability-enhancing, angiogenic, and endothelial cell-specific mitogenic activities.<sup>1,4,5</sup> Young age, low BMI, high doses of exogenous gonadotropins, high rate of increase of serum estradiol levels, and previous episodes of OHSS are some of the risk factors associated with OHSS.<sup>6</sup>

OHSS has been classified based on severity as follows:

- Grade 1 - Abdominal distension and discomfort.
- Grade 2 - Grade 1 disease plus nausea, vomiting and/or diarrhoea plus ovarian enlargement from 5 to 12 cm
- Grade 3 - Grade 2 plus evidence of ascites on ultrasound
- Grade 4 - Grade 3 with clinical evidence of ascites and/or hydrothorax and breathing difficulties
- Grade 5 - All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities and diminished renal perfusion and function

Grades 1 and 2 are regarded as mild, grade 3 as moderate, and grades 4 and 5 as severe OHSS.<sup>7</sup>

The treatment is based on the degree of hyperstimulation. Mild OHSS requires only supportive care, but can progress to moderate or severe form if conception ensues. These patients are observed for increasing abdominal girth, sudden weight gain, and abdominal discomfort for at least 2 weeks or until menstrual bleeding occurs. Patients with moderate OHSS are mainly observed and advised adequate fluid intake, rest and ultrasonographic evaluation of ovarian cyst size. Serum electrolytes, hemoconcentration and renal parameters should be regularly monitored. Severe OHSS is dangerous and can be life threatening. Patients are advised rest, and abdominal girth and weight are measured daily. Fluid balance should be assessed every 4 hours. Intravenous infusion with normal saline (125 to 150 ml/hour) is administered with monitoring of urine output. However, fluid overload should be avoided. Albumin infusions should be given in case of hypoalbuminemia and unsatisfactory urine output. The use of diuretics may be counterproductive in case of decreased urine output. Subcutaneous heparin is administered to prevent thrombosis. Abdominal paracentesis may be required in case of severe abdominal pain or discomfort, or if the patient has renal or pulmonary compromise. Surgery is indicated only if the patient has ovarian torsion, ruptured cyst or internal haemorrhage.<sup>1</sup>

Prevention of OHSS is mainly by reducing the exposure to gonadotropins, cycle cancellation (withholding hCG in ovulation induction), coasting (decreasing or withholding gonadotropin in case of high serum estradiol levels with a large number of follicles during stimulation, with continuation of gonadotropin releasing hormone GnRH agonist) and modification of the ovulation triggering agent (replacement of hCG by exogenous or endogenous luteinizing hormone). The prophylactic administration of albumin may interrupt the development of OHSS by increasing the plasma oncotic pressure and binding the mediators of ovarian origin. Hydroxyethyl starch solution may be a substitute for albumin as it holds less chances of viral transmission when compared to albumin infusions. Cryopreservation of all embryos may be possible but there is no sufficient data to support this approach.<sup>1,8</sup> A Cochrane review has demonstrated that the incidence of severe OHSS was significantly lower in GnRH antagonist protocol than in GnRH agonist protocol.<sup>9</sup> The use of progestogens instead of hCG for luteal phase support can also reduce the incidence.<sup>10</sup> In vitro maturation of oocytes offers great potential for OHSS prevention in high risk patients.<sup>11</sup> Dopamine agonist like cabergoline partially inhibits the VEGF receptor 2 phosphorylation levels and its associated vascular permeability without affecting luteal angiogenesis, thereby reducing the onset of OHSS.<sup>12</sup> The use of low-dose aspirin was associated with reduction in the OHSS in a high-risk group.<sup>13</sup> Meloxicam was found to be useful in OHSS associated ovarian weight and expression of VEGF in animal models.<sup>14</sup> Controlled ovarian hyperstimulation with gonadotropins may lead to a higher risk of OHSS for patients affected by PCOS, due to high sensibility and exaggerated response to gonadotropins.

Recombinant FSH is a new alternative for ovulation induction for in vitro technique. FSH can be obtained by purifying urine from menopausal women and followed by extraction of FSH and LH. But the presence of LH may have a negative effect on ovulation induction. Hence, pure FSH is obtained by recombinant DNA technique. Previously human menopausal gonadotropin (hMG) was used for controlled ovarian hyperstimulation, which contains both LH and FSH purified from menopausal women's urine. Though more follicles can be developed, there is a premature surge of LH, thereby causing premature luteinisation in response to increasing estrogen concentration. Another negative effect is OHSS. The use of recombinant FSH was found to be a successful method for in vitro fertilization.<sup>15,16</sup> In case of PCOS, the treatment results with hMG are not encouraging.<sup>17</sup> However, the use of recombinant FSH was found to be useful in PCOS.<sup>18</sup> Though OHSS is seen with recombinant FSH, the use of low dose FSH for ovulation induction in PCOS is safe, has high pregnancy rate and low risk of multiple pregnancies.<sup>19-21</sup>

## CONCLUSION

OHSS may be considered as the most serious and life threatening complication related to assisted reproduction techniques. Preventing or minimizing the risk of OHSS is a cornerstone, especially for those women considered to be at high risk. Our patient had a low BMI and was given controlled ovarian hyperstimulation with low dose recombinant-FSH. Yet, she developed severe OHSS after ovulation induction with hCG, which is an uncommon scenario. She also achieved pregnancy, making the situation more serious. Hence, in the setting of risk factors, OHSS should be anticipated even with low dose recombinant-FSH. Patients should be identified at an early stage and treated urgently in order to avoid fatal complications.

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**Authors Contribution:**

**RGM**- Concept and design, manuscript preparation, revision of manuscript and treating physician; **SVK**- Revision of manuscript and treating Infertility Specialist; **NV**- Revision of manuscript and treating Pulmonologist.

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