CASE SERIES

Ovarian Hyperstimulation Syndrome in Voluntary Ovum Donors: A Case Series

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ABSTRACT

Aim: The aim of this study was to report a case series of ovarian hyperstimulation syndrome in voluntary oocyte donors and discuss their management and clinical course.

Background: Ovarian hyperstimulation syndrome is a rare, iatrogenic complication occurring in artificial reproductive technology cycles. Recently, with the boost in the use of oocyte donors in ART, it has been noted that voluntary oocyte donors who undergo controlled ovarian hyperstimulation to induce superovulation in them are increasingly suffering from this syndrome. This syndrome varies from mild-to-severe and may become potentially lethal, the pathophysiologic hallmark of which is the accumulation of massive extravascular exudate combined with profound intravascular volume depletion.

Case description: Seven voluntary oocyte donors who have undergone multiple cycles of superovulation and oocyte retrieval presented with moderate-to-severe ovarian hyperstimulation syndrome (OHSS) and required admission. Clinical examination and ultrasonography confirmed the diagnosis of ovarian hyperstimulation syndrome. Most of these patients were optimally managed by conservative methods while two developed complications and required emergency laparotomy.

Clinical significance: With proper precautions and early detection, the deleterious effects of this condition can be prevented, and progression to a life-threatening ailment can be avoided. Donors must be thoroughly investigated and their donations must be well-spaced to avoid these negative impacts on their health. Understanding this condition will allow better management of donors at ART centers and prompt recognition of such complications by the clinician.

Keywords: Assisted reproductive technology cycles, Ovarian hyperstimulation syndrome, Ovum donor.

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BACKGROUND

There has been exponential growth in the use of donated oocytes in infertility treatment. The first successful use of donor eggs occurred in Australia in 1983. In the 35 years after that achievement, the demand for donor oocytes for artificial reproduction expanded dramatically, almost two times between 2000 and 2010. Several factors play a role in the increasing demands for oocyte donation: an increase in delayed childbearing and desire for parenthood among same-sex couples and single people. These donors are subjected to hormonal treatment by the fertility centers to induce superovulation. Ovarian hyperstimulation syndrome in varying severity is an infrequent, iatrogenic complication occurring in women who undergo controlled ovarian hyperstimulation with human gonadotropins. These patients have a high response to hormonal medications and resulting in large ovaries, loss of fluid from intravascular space leading to ascites, hydrothorax, and vascular thrombosis. Here, the authors report moderate-to-severe cases of ovarian hyperstimulation syndrome in voluntary donors of oocytes.

CASE DESCRIPTION

Cases 1–5

Table 1 describes the five cases that were managed conservatively.

An observational study was conducted in a tertiary care hospital where seven cases of ovarian hyperstimulation syndrome were studied. Five cases had more or less similar complaints and were managed conservatively while two cases had more ominous manifestations and required surgical intervention (Fig. 1).

All the above patients were admitted for medical management. Patients were weighed and abdominal girth was taken daily and charting was done. Strict input output monitoring was done. Hydration was maintained by intravenous (IV) fluids. IV ceftriaxone 1 gm twice daily (BD) and IV metronidazole 500 mg 3 times a day (TDS) for 7 days. IV paracetamol or IV tramadol for pain relief. IV ondansetron 4 mg TDS as antiemetics. Inf. Low-molecular-weight heparin (LMWH) 40 mg SC OD from thromboprophylaxis. Cabergoline 0.5 mg OD was given for 7 days. All five patients showed clinical improvement in 7–10 days, with diuresis, decrease in weight heparin (LMWH) 40 mg SC OD from thromboprophylaxis. Cabergoline 0.5 mg OD was given for 7 days. All five patients showed clinical improvement in 7–10 days, with diuresis, decrease in weight

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in ovarian size but on day 14 showed a significant reduction in the volume of ovaries and no ascites. Above is a table showing the variation in ovarian volume on the day of admission and day 14.

Table 2 represents the difference in ovarian volume before and after treatment in five cases.

However, if there is undue delay in diagnosis or seeking medical help for the condition, ovarian hyperstimulation can manifest dreaded complications in the patient and can also be fatal. We had two cases that required surgical management for OHSS and described as follows.

**Case 6**

A 30-year-old P3L3 was referred from a private clinic with a scan suggestive of OHSS with anuria for 2 days. She had a history of being a voluntary ovum donor and undergoing hormonal treatment at an *in vitro* fertilization (IVF) center. Four days after the pickup, the patient developed abdominal distension, pain, and breathlessness, and over the next 2 days patient’s urine output reduced till she became anuric on day 6 post pickup.

On examination: The patient was vitally stable, with a respiratory rate of 36/min, generalized edema, and a grossly distended abdomen.


Ultrasongraphy (USG) was suggestive of OHSS with bilateral pleural effusion. As multiple organs were involved,
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the patient was admitted to the intensive care unit. On day 3 of admission, the patient’s hemoglobin dropped to 4.4 gm/dL. Ultrasound revealed moderate ascites with multiple echoes. Ascitic tap revealed hemoperitoneum. The patient was taken for an exploratory laparotomy. Intraoperatively, there was a rupture of the left ovarian cyst capsule and partial torsion of the left ovarian cyst pedicle (Fig. 2). The right ovary was also enlarged in size with multiple cysts. Left oophorectomy was done. The patient was kept in ICU postoperatively. She underwent five cycles of hemodialysis. However, her condition failed to improve and she succumbed on day 10 of surgery.

Case 7
A 29-year-old P2L2 presented with acute pain abdomen and multiple episodes of vomiting. She had a history of undergoing one cycle of controlled ovarian hyperstimulation (COH) for oocyte donation at an IVF clinic 6 days ago. Urgent ultrasonography was done that revealed bilateral bulky ovaries with torsion of the left ovary. The patient was taken for emergency exploratory laparotomy with left oophorectomy. Her condition improved postoperatively and the patient was discharged on day 5 in stable condition.

Discussion
The OHSS is reported in almost 1–14% of IVF cycles. Moderate cases of OHSS are roughly 3–6% while the serious life-threatening form that leads to hospitalization occurs in 0.13%. The incidence and severity of OHSS may be lower in oocyte donors, partly owing to the absence of conception after stimulation. Ovarian hyperstimulation syndrome can be early or late. The cases that present within 9 days of exogenous human chorionic gonadotropin (HCG) injection and called early OHSS and cases that present after 10 days are categorized as late OHSS and are due to endogenous estrogen production.

The ovarian hyperstimulation syndrome is classified in five grades as per the severity according to Golan’s classification.

Mild OHSS, Grade 1 – Distension of abdomen

Grade 2 – Grade 1 disease with nausea and/or diarrhea with ovarian enlargement from 5 to 12 cm.

Moderate OHSS, Grade 3 – Signs of mild OHSS and ultrasonography suggestive of ascites.

Severe OHSS, Grade 4 – Signs of moderate OHSS and ascites and/or hydrothorax and respiratory difficulties.

Grade 5 – All signs of grade 4 disease and hemoconcentration, coagulation abnormalities, and diminished renal function.

In our case series, most cases presented on the milder side of the spectrum with abdominal distention, nausea and vomiting, and ascites (cases 2–4). These patients did not have multiple organ involvement or hemoconcentration and were classified as grade 3. They were managed symptomatically and monitored for signs of deterioration. In cases 1 and 5, the OHSS was associated with hydrothorax and hemoconcentration and hence were graded as grade 5. We successfully managed the case with IV antibiotics and IV analgesics, antiemetics, and anticoagulants. In a similar case reported in Turkey of grade 4 OHSS, the patient had undergone transvaginal ultrasound-guided ascitic fluid draining of 2 L of fluid to relieve pain abdomen and dyspnea. The patient also received 20% human albumin solution. Another case reported in East Africa had given per vaginal progestin preparation along with IV antibiotics, and analgesics. The LMWH had favorable results, and their patient was discharged with per vaginal progestin. All patients of grade 5 OHSS were managed in intensive care setup, and so were our patients.

It is rare for patients of the OHSS to present as an acute emergency and require surgical management, but cases 6 and 7 in the present series required operative intervention. Surgical intervention is required if there is torsion of the bulky ovaries or rupture of cysts. We had opted for exploratory laparotomy in both cases due to these complications. However, as the patient in case 6 has multiple organ dysfunction, we lost the patient on day 10 of surgery. A similar case of OHSS with torsion was diagnosed in a 40-year-old patient in her sixth week of pregnancy conceived following IVF treatment. The laparoscopic ovarian detorsion was done for the same. To prevent complications associated with repeated oocyte donations and to prevent exploitation of the donors, The Assisted Reproductive Technology Regulation Act, 2021, states that an ovum donor can donate oocytes only once in her entire life, and that too not more than seven oocytes to be retrieved from the oocyte donor in that particular cycle.

Conclusion
It is crucial to identify risk factors and adopt preventive strategies both prior to and at the time of stimulation. Donors with polycystic ovarian syndrome (PCOS) and high responders are at a greater risk for the OHSS; therefore, ovulation induction in patients with PCOS should be initiated with the least possible gonadotropin dose. Aromatase inhibitors for ovulation induction have fewer chances for the OHSS and are preferred in PCOS. Women considered at higher risk of developing OHSS should be induced with low doses of gonadotropin and preferably co-treated with gonadotropin-releasing hormone (GnRH) antagonist. Serum estradiol monitoring is helpful in predicting risk of the OHSS. A quick rise in estradiol levels and serum estradiol concentrations >2500 pg/mL, increased antimonial hormone (AMH) >3.35 ng/mL, and antral follicular count (AFC) >14 follicles of 11 mm size (hyper-responders) are important predictive factors. Implementing screening of donors for these factors helps in early recognition, and management of OHSS, reduction in the incidence of OHSS, and related morbidity and mortality.

Fig. 2: The intraoperative finding in a case of OHSS complicated by cyst rupture
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