# Ovarian Hyperstimulation Syndrome: Observation in 21 patients

*Fathi E. Al-Jama, CAB, (Ob/Gyn)**

**Objectives: To identify patients with Ovarian Hyperstimulation Syndrome (OHSS) and highlight their management.**

**Design: A retrospective study of 21 patients with OHSS over a period of seven years was undertaken.**

**Setting: Department of Obstetrics and Gynaecology, King Fahad Hospital of the King Faisal University, Al-Khobar, Saudi Arabia.**

**Subjects: Twenty one symptomatic patients admitted to the hospital and diagnosed to have OHSS following ovulation induction treatment in the surrounding clinics and hospitals of the region.**

**Results: OHSS developed in 21 patients during the first to the eighth treatment cycle. The symptoms and signs of hyperstimulation appeared in most patients within 3-7 days of injection of human chorionic gonadotropin. Four patients in the series had associated pregnancy (one triplets). The treatment given was mainly conservative.**

**Paracentesis was performed in six patients. Four patients required management of their condition in the intensive care unit. Two patients needed chest drainage for pleural effusions Surgical intervention for acute abdomen was carried out in two patients. No patient died in the series.**

**Conclusion: Since OHSS is iatrogenic in nature, its prevention or reduction of severity may be achieved by restricting the use of drugs for induction of ovulation to only specialists who can identify the women at risk of developing OHSS, regulate the dose/response of the patient and have facilities and capabilities to treat complications if and when they arise. Indiscriminate use of ovulation induction drugs by general practitioners should be abandoned.**

***Bahrain Med Bull 1999;21(3): 80-84***

Induction of ovulation with gonadotropins is an integral part of modern assisted conception programs. The use of these exogenous gonadotropins has rapidly increased in recent years. Besides the highly specialised centres treating infertility, gynaecologists and general practitioners too are prescribing these medications extensively without appreciating that they are fraught with danger to the patient. The most dangerous complication of ovarian hyper stimulation syndrome (OHSS) is reported to be 1-10% in treatment cycles of patients having in-vitro fertilisation (IVF),[1,2] and in less than 4% of cycles treated for anovulation[3]. The purpose of this study is to highlight the management of patients with OHSS admitted to the King Fahad Hospital of the University, Al-Khobar, between July, 1991, and June 1998 and to emphasize the serious complications that may result from the injudicious use of ovulatory drugs by doctors in the region.

## METHODS

The case records of 21 patients with OHSS who were admitted to the hospital as an emergency during the period of study were analyzed retrospectively. The demography, dosage of the ovulatory drugs received by the patients, symptoms and signs on admission, investigations and treatment of the complications in the hospital were noted. The age, parity and treatment received for induction of ovulation in 21 patients who were admitted with the diagnosis of OHSS is shown in Table 1. Only two patients were treated at the author's institution while the remaining patients received therapy by physicians in the surrounding clinics and hospitals.

* Assitant Professor & Consultant
King Fahad Hospital Al Khobar &
King Faisal University
Dammam, Saudi Arabia

**Table 1. Demography and ovulatory drugs receved in 21 patients**

| Patient No. | Age (yars) | Parity | Duration of infertility (yrs) | Pergonal (no. of amps) | Clomid (mg) | hCG (units) | No. of cycles |
|---|---|---|---|---|---|---|---|
| 1 | 28 | P1+0 | 3 | 29 | - | 10000 | 5 |
| 2 | 34 | P1+0 | 10 | 10 | 500 | 10000 | 2 |
| 3 | 22 | P0+2 | 3 | 20 | - | 10000 | 3 |
| 4 | 25 | P0+0 | 5 | 14 | - | 10000 | 3 |
| 5 | 32 | P0+0 | 9 | - | 1000 | 5000 | 8 |
| 6 | 31 | P3+0 | 5 | 16 | 500 | 10000 | 1 |
| 7 | 36 | P0+0 | 7 | 12 | - | 10000 | 2 |
| *8 | 18 | P0+0 | 6 | - | 1000 | - | 3 |
| 9 | 31 | P0+0 | 10 | 9 | 1250 | - | 2 |
| 10 | 27 | P0+2 | 6 | 10 | 500 | 5000 | 2 |
| *11 | 30 | P3+1 | 4 | 3 | 1250 | - | 2 |
| 12 | 28 | P0+0 | 3 | - | 1000 | 10000 | 1 |
| 13 | 31 | P1+0 | 4 | 8 | _ | _ | 2 |
| 14 | 24 | P0+0 | 2 | 16 | - | 10000 | 2 |
| 15 | 21 | P0+0 | 2 | 8 | 750 | 10000 | 2 |
| 16 | 22 | P0+0 | 3 | 10 | 1000 | 10000 | 3 |
| 17 | 23 | P0+0 | 4 | 4 | 750 | 5000 | 5 |
| 18 | 25 | P0+0 | 6 | 20 | - | 10000 | 2 |
| 19 | 27 | P0+2 | 5 | 16 | 1000 | 10000 | 8 |
| 20 | 31 | P1+0 | 7 | 12 | 750 | 10000 | 4 |
| 21 | 29 | P0+1 | 4 | 24 | - | 10000 | 2 |

* Patients treated at the author's institution

OHSS was defined as a cystic enlargement of the ovary of 5cm or more in diameter with symptoms during the treatment cycle of anovulation, with or without ascites. The original classification of OHSS included only three categories (mild, moderate and severe),[4] while Golan et al reclassified OHSS into five grades of severity[3]. Recently Navot et al[5], added a critical state in that classification of OHSS (Table 2)[5]. Ovarian enlargement is a constant feature of OHSS with massive enlargement in severe OHSS (>12 cm diameter).

**Table 2: Classification of severity of OHSS**

| Grade of OHSS | Clinical Features |
|---|---|
| MILD | |
| Grade 1 | Abdominal distention and discomfort, |
| Grade 2 | Grade 1 plus nausea, vomiting and/ or diarrohoea. |
| MODERATE | |
| Grade 3 | Features of mild OHSS plus ultrasonic evidence of ascites. |
| SEVERE | |
| Grade 4 | Moderate OHSS plus massive ascites ± hydrothorax or oliguria, haematocrit > 45 per cent, liver dysfunction, creatinine clearance ≥ 50 ml/min |
| CRITICAL (life threatening) | |
| Grade 5 | Tense ascites ± hydrothorax, oliguria, renal failure, thromboembolic phenomena or ARDS. Haematocrit >55 percent, creatine clearance <50ml/min. |

From Golan et al[3] and Navot et al[5]

Five patients (23.8 %) in the series were critically ill, while the remaining 16 patients had moderate to severe OHSS.

Three treatment groups were identified in the series:

**Group 1:** patients who received clomiphene citrate (clomid), pergonal (hMG) and human chorionic gonadotropin (hCG).

**Group 2:** patients treated with pergonal and hCG.

**Group 3:** patients treated with clomiphene citrate and hCG. The dose of clomiphene citrate used was up to 250mg daily for 5 days, pergonal 2-4 ampoules daily for up to 10 days in combination with hCG 5-10,000 IU given intramuscularly between the 11th and 14th day of the cycle .

Unfortunately, the majority of patients did not know the results of their pre-treatment investigations, nor had they any monitoring of ovarian follicles or hormonal assays during the treatment cycles. Two of the patients who developed moderate OHSS following treatment in our hospital for infertility had thorough evaluation before treatment for anovulation began. These included semen analysis, post-coital tests, appropriate serum hormonal assays, pelvic ultrasonography, hysterosalpingography and/or laparoscopy and dye studies. They also had regular serum estradiol measurements and ultrasonic ovarian follicle size estimation to adjust individually the dose of gonadotropins and the length of treatment required by the patient.

## RESULTS

Seven of the 21 patients in the series were found to have sonographic features similar to PCO of small peripherally placed follicles with an echo dense stroma (necklace sign)

before induction of ovulation. There were 10 patients with OHSS in group 1, 8 in group 2 and 3 patients in group 3 (Table 1). Two patients in group 1 developed OHSS during the first treatment cycle, 4 during the second and 4 patients during the third to eighth treatment cycle. Five patients in group 2 had only two treatment cycles when they developed OHSS, two in the third and one in the fifth cycle. In group 3, one patient developed OHSS in the first treatment cycle with conception of triplets.

**Table 3. Presentation and management of the 21 patients with OHSS**

| Patient no. | Conception | Clinical Symptoms | Physical Findings | Management | | Hospital stay in days |
|---|---|---|---|---|---|---|
| | | | | Coservative | Surgical | |
| 1 | + early abortion | Abd pain & distention, dyspnoea | Massive ascities, bil.ov. Cysts 10x8 cm | + paracentesis ICU | – | 30 |
| 2 | – | Abd pain & distention | Bil.ov. Cysts 9.6 x 7.6 cm | – | – | 8 |
| 3 | + early abortion | Vomitting, Abd pain, SOB, palpitation | Ascites with acute abd. Ovaries 10.5 x 7 cm | ICU Paracentesis | Laparotomy for ruptured ov.cysts and IP hem | 38 |
| 4 | – | Lower Abd pain, dyspnoea & palpitaion | Air entry, pleural effusion ovaries 11 x 6 cm each | Chest tube in ICU paracentesis | – | 25 |
| 5 | – | Acute lower abd pain nausea & vomiting | Both ovaries 7x6 cm | + | – | 10 |
| 6 | – | Severe lower abd pain, distention,, orthopnea & chest pain | Bil ov cyst 10.5 x 10.6 cm | + | – | 12 |
| 7 | – | Lower abd pain | Bil ov cyst 10 x 6 cm | + | – | 6 |
| 8 | – | Lower abd pain | Bil ov cyst 8 x 6.5 cm | + | – | 5 |
| 9 | – | Lower abd pain | Bil ov cyst 8 x 7 cm | + | – | 5 |
| 10 | – | Lower abd pain | Bil ov cyst 10 x 11 cm | + | – | 12 |
| 11 | – | Lower abd pain | Bil ov cyst 9 x 7.5 cm | + | – | 7 |
| 12 | + triplets | Severe lower abd pain & distention, nausea | Right ov cyst 14 x 9 cm | + | – | 15 |
| 13 | – | Severe lower abd pain & vomiting | Bil ov cyst 9 x 8 cm | + | – | 4 |
| 14 | – | Severe lower abd pain, nausea, vomiting & dyspnea | Acute abd, pleural effusion, massive ascites, Bil. ov cysts 10 x 10 cm | Chest tube in ICU, Paracentesis | – | 22 |
| 15 | + Delivered at | Lower abd pain & distention | Bil ov cyst 17 x 10 cm | + | – | 10 |
| 16 | – | Abd pain, nausea & vomiting | Bil ov cyst 12 x 6.2 cm | + | – | 4 |
| 17 | – | Lower abd pain & distention | Bil ov cyst 10 x 7 cm | + | – | 5 |
| 18 | – | Severe abd pain & vomiting | Massive ascites, Bil ov cysts 15 x 10 cm | Paracentesis | Laparato my for torsion left ov. cyst | 15 |
| 19 | – | Lower abd pain & distention | Mild ascites, pleural effusica. ovaries 12 x 8 cm | + | – | 12 |
| 20 | – | Severe abd pain & nausea | Mild ascites, Bil ov, cysts 10 x 8 cm | + | – | 10 |
| 21 | – | Severe abd pain & distention | Both ovaries 14 x 10 cm fluid in POD | + | – | 14 |

*Abd: abdomen; Bil: Bilateral Ov: Ovarian; IP Hem: Intraperitoneal Haemorrhage; POD: Pouch of Douglas; SOB: Shortness of breath*

The clinical manifestations and management of the patients with OHSS are shown in table 3. The symptoms and signs appeared in most cases within 3 to 7 days of injection of hCG. Four patients in the series had associated pregnancy; two patients were from group 1, one from group 2 and one patient, from group 3 (triplets). The obstetric outcome of the pregnancies with OHHS were two early abortions, one singleton delivery at term and one triplet delivery at 34 weeks.

Haemoconcentration [increased haematocrit (Hct) values between 5-8%] was observed in 12(57%) patients, six of whom also showed increased serum osmolality. Four patients showed hyponatremia and one, hypoalbuminemia. Coagulation profile such as coagulation time, bleeding time, prothrombin and serum fibrinogen were found to be within normal limits except in one patient (No 21) without any consequence.

The treatment regimen given to these patients was mainly conservative. After hospitalisation, the patients were kept on strict bed rest. The vital signs were monitored frequently and the fluid intake and output were charted. The initial investigations included complete blood count, serum urea, electrolytes, clotting profile, renal and liver function tests, patient body weight and pelvic ultrasound scan to assess the extent of ovarian enlargement, the size and number of luteal cysts and the presence of fluid in the pelvis and abdomen. Intravenous fluid therapy consisted of crystalloids approximately 3 liters per 24 hours. Where the serum albumin was less than 32g/L or Hct greater than 45%, 2 units of human serum albumin (HSA) were given with 2 liters of crystalloids per 24 hours. HSA increases plasma oncotic pressure thereby raising intravascular volume and encouraging fluid shift out of the third space. The fluid therapy was monitored by the patient's response to rehydration and daily measurements of serum albumin and electrolytes. Insertion of a central venous pressure line was required in four patients. The severity of the condition was monitored by daily clinical examination of the heart, chest and abdomen along with measurements of abdominal girth, body weight and Hct. No patient in the, series required anticoagulant therapy. Paracentesis was performed in six patients (28.6%) under ultrasonic guidance to alleviate the patients' discomfort and breathing difficulties from tense ascites. Two patients required chest drainage for pleural effusion. Four patients were treated initially in the intensive care unit (ICU) for adult respiratory distress syndrome. The acute symptoms in the patients subsided within several days while regression of the ovarian cysts required a longer period ranging from 20 to 40 days.

Two patients required surgical intervention for acute abdominal pain. Laparotomy revealed rupture of the ovarian cyst with intraperitoneal hemorrhage in one patient (No.3) and torsion of the ovarian cyst in the other patient (No.18) requiring removal of the affected ovary in both the patients. Histology of the ovaries revealed multiple follicular cysts, corpora lutea with hemorrhage and stromal edema.

## DISCUSSION

OHSS is a well-known iatrogenic complication of the treatment of ovulation induction with hMG, clomiphene citrate and hCG. The most florid form of this syndrome is characterised by gross ovarian enlargement, massive ascites, hydrothorax, hypovolemia, haemoconcentration, oliguria and thromboembolic episodes. The incidence of this severe form of hyperstimulation varies from 0.5 - 2% among all IVF cycles[4]. Although the severe form is rare, it still has serious consequences on the patients' health causing severe morbidity and even death of the patient. The largest epidemiological study carried out in Belgium to identify pretreatment characteristics of women at greatest risk of OHSS after assisted conception confirmed the association of PCOS and PCO appearance of ovaries on ultrasound scan (necklace sign) in the absence of endocrine features of PCOS. Other risk factors identified for OHSS to develop are young age and lean habitus, exaggerated ovarian response to gonadotropin therapy and the use of hCG to trigger ovulation[7,8]. The pathogenesis of OHSS is unknown, albeit the Renin-Angiotensin system is believed to be the predominant biochemical mediator. Acute shift of the body fluid from the intravascular compartment may result in ascites, hydrothorax and even generalised edema. This shift of the body fluid is the main cause of morbidity and mortality in OHSS. Treatment is aimed at prompt correction of the intravascular volume with appropriate crystalloid or colloid fluid and electrolyte replacement, thus preventing haemoconcentration and hypovolemia.

It is therefore of utmost importance that physicians prescribing these drugs be familiar with all the possible complications and their management. Pretreatment assessment of the patient by ultrasonography of the ovaries and endocrine assay during the early follicular phase is essential to identify PCO. Treatment with gonadotropins should be monitored by serial estradiol measurements and/or by serial vaginal ultrasonography starting from the 7th or 8th day of treatment.[9]

Women developing mild OHSS may be followed up in the outpatient clinic with advice to increase intake of oral fluids. Those with moderate/severe OHSS should be hospitalised to regulate fluid and electrolyte balance. The urine output should be carefully monitored. Paracentesis under ultrasound guidance to avoid injury to the bowel and enlarged ovaries, is required when there is tense ascites causing respiratory embarrassment. Sometimes acute respiratory distress due to pleural effusion may require drainage by pleural tap. If pregnancy has not occurred, the majority of the women with severe OHSS begin to recover by the mid-luteal phase and complete recovery usually occurs with the onset of the next menstrual period. However, the illness may be more prolonged in women who have associated pregnancy with OHSS.[5,10] In life-threatening OHSS the only option may be to terminate the pregnancy either surgically or medically.

Surgical intervention is only undertaken when there is clear evidence of torsion or rupture of the ovarian cyst and the operative procedure should be as conservative as possible

with gentle handling of the ovaries as they are very friable[11]. There is a real possibility of patients being castrated by the inexperienced operator who is unfamiliar with the syndrome and is suddenly confronted with these large ovaries[3,12].

## CONCLUSION

**Since OHSS is iatrogenic in nature, its prevention can be achieved only by identifying the women at risk of developing this syndrome and modifying or withdrawing the trigger factor that causes the disease. It may be emphasized that drugs for ovulation induction should not be prescribed indiscriminately by the general practitioners. Its use should be restricted only to specialists who have the knowledge and facilities to regulate the dose/ response in the patient and are capable of treating complications as soon as they arise thereby reducing the severity and morbidity of OHSS.**

## REFERENCES


1. Forman RG, Frydman R, Egan D. Severe ovarian hyperstimulation syndrome using agonists of gonadotropin releasing hormone for in vitro fertilisation: a European series and a proposal for prevention. Fertil Steril 1990;53:502-9.
2. MacDougall MJ, Tan SL, Jacobs HS. In vitro fertilisation and the ovarian hyperstimulation syndrome. Hum Reprod 1992;7:579-600.
3. Golan A, Ron-El R. Herman A, et al. Ovarian hyperstimulation syndrome; and update review. Obstet Gynecol Surv 1989;44:430-40.
4. Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey Fertil Steril 1978;30:255-68.
5. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249-61.
6. Delvinge A, Demoulin A, Smitz J, et al. The ovarian hyperstimulation syndrome in invitro fertilisation: a Belgian multicentric study. Clinical and biologic features. Hum Reprod 1993;8:1353-60
7. Mathur RS, Joels LA, Akande AV, et al. The prevention of ovarian hyperstimulation syndrome. Br J Obstet Gynaecol 1996;103:740.
8. MacDougall MJ, Tan SI, Balen AH, et al. A controlled study comparing patients with or without polycystic ovaries undergoing in vitro fertilisation. Hum Reprod 1993;8:233-37
9. Brinsden PR, Wada 1. Tan SL, et al. Diagnosis, prevention and management of ovarian hyperstimulation syndrome. Br J Obstet 1995;102:767-72.
10. Wada I, Matson PL, Troup SA, et al. Assisted conception using buserelin and human menopausal gonadotrophins in women with polycystic ovary syndrome. Br Obstet Gynaecol 1993b;100:365-69.
11. Rizk B, Meagher S, Fisher AM. Severe ovarian hyperstimulation syndrome and cerebrovascular accidents. Hum Reprod 1990;5:697-98.
12 . Engel T, Jewelewicz R, Dyrenfurth I, et al. Ovarian hyperstimulation syndrome. Report of a case with notes on pathogenesis and treatment, Am J Obstet Gynecol 1972;112:1052-60.