OVULATION INDUCTION

Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis

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Objective: To describe our experience with aggressive outpatient transvaginal paracentesis to manage ovarian hyperstimulation syndrome (OHSS).

Design: Retrospective case series.

Setting: Private, academically affiliated IVF center.

Patient(s): Women undergoing assisted reproductive technologies (ART) and having a diagnosis of OHSS. Intervention(s): Management of OHSS with hospitalization or outpatient transvaginal paracentesis between 1999 and 2007.

Main Outcome Measure(s): Grade and stage of OHSS, need for hospitalization, and adverse events.

Result(s): From 1999 to 2007, we identified 183 patients with OHSS. We began performing outpatient transvaginal paracentesis to treat OHSS in 2002. We have performed 146 outpatient transvaginal paracenteses in 96 patients with no procedure-related complications. With the implementation of early, aggressive, outpatient paracentesis, the number of patients requiring hospitalization for OHSS decreased. From 2006 to 2007, 29 patients were diagnosed with severe OHSS and 25 (86%) were managed as outpatients with transvaginal paracentesis with no complications.

Conclusion(s): This report represents one of the largest series of patients with OHSS managed with outpatient transvaginal paracentesis. Although there continues to be a small percentage of patients with OHSS who require hospitalization, the vast majority of patients with severe OHSS at our center in the past 2 years had their condition successfully managed as outpatients with use of aggressive transvaginal paracentesis. (Fertil Steril® 2009;92:1953-9. ©2009 by American Society for Reproductive Medicine.)

Key Words: Ovarian hyperstimulation syndrome, paracentesis

Ovarian hyperstimulation syndrome (OHSS) is among the most serious iatrogenic complications of pharmacologic ovulation induction. It is potentially life threatening and, unfortunately, despite increased awareness of well-known prognostic variables OHSS may not always be prevented (1). The pathophysiology of OHSS involves increased capillary permeability to plasma proteins leading to intravascular volume depletion with fluid shift to the extravascular compartment (2, 3). These changes have been suggested to be mediated by vasodilatory, inflammatory, and angiogenic substances

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released by the stimulated ovaries including renin, prorenin, angiotensin I and II, interleukin-6, interleukin-8, and vascular endothelial growth factor (4-9). Clinically, this fluid shift may be manifested by ascites, pleural effusions, oliguria, hemoconcentration, and electrolyte abnormalities.

Several staging systems have been established to classify OHSS as mild, moderate, and severe with further division into grades of severity (10-12). Mild OHSS is considered to be of minimal consequence, involving some degree of abdominal bloating or discomfort, weight gain, and mild gastrointestinal symptoms. Ultrasound evaluation in mild OHSS may reveal enlarged ovaries (>5 cm diameter). Moderate OHSS involves more pronounced pain, nausea, abdominal distension, gastrointestinal symptoms, and enlarged ovaries by ultrasound examination and, importantly, includes sonographic evidence of ascites but normal laboratory parameters. Severe OHSS is characterized by all of the features of mild and moderate OHSS with the addition of clinical evidence of third-spaced fluid in the peritoneal or pleural cavities. Severe OHSS may be complicated further by laboratory abnormalities including hemoconcentration, electrolyte



imbalance, acute renal insufficiency, hepatic dysfunction, and coagulopathy (12-14). In very rare cases, severe OHSS may be fatal (15). The incidence of severe OHSS is estimated to range from 0.5% to 5% per cycle (13). A large study from Finland of 9,175 IVF cycles demonstrated that, in at least 2.4% and up to 3.6% of women in each cycle, OHSS developed that was severe enough to warrant hospitalization (16).

The management paradigm of OHSS varies dramatically in the literature. Some authors mandate hospitalization in all patients in whom severe OHSS is diagnosed or all patients with a hematocrit >45% (12, 15–19). Others recommend the addition of inpatient paracentesis to IV rehydration to drain ascites fluid in select cases of severe discomfort, pulmonary compromise, or renal compromise not responding to conservative management (20, 21). Still others assert that outpatient paracentesis can be used to minimize or avoid hospitalization altogether (22, 23).

On the basis of the divergent management approaches toward OHSS in the literature, our goal was to describe our experience with the aggressive use of outpatient transvaginal paracentesis in the management of patients with OHSS at a private, academically affiliated IVF center over a 9-year period. We hypothesized that outpatient transvaginal paracentesis, when performed early and aggressively in the treatment of OHSS, had been used to safely manage the condition of patients with even severe OHSS and was associated with fewer inpatient hospitalizations.

MATERIALS AND METHODS

A single author (L.P.S.) reviewed the medical records of all patients from Boston IVF (Waltham, MA) who were hospitalized at our affiliated institution Beth Israel Deaconess Medical Center (Boston, MA), who received outpatient transvaginal paracentesis, or whose condition was managed with outpatient observation alone for OHSS from January 1, 1999, through December 31, 2007. There were no exclusion criteria. Collected data included age, medical history, type of assisted reproduction protocol, peak E₂ level, symptoms, ultrasound findings, laboratory results, and pregnancy outcome. If applicable, number of days hospitalized, chest x-ray examination findings, number of inpatient transabdominal paracenteses, number of inpatient thoracenteses, volume of fluid removed, number of outpatient transvaginal paracenteses, and complications were recorded. In all patients for whom the data were available, the stage and grade of OHSS were classified according to the criteria proposed by Whelan and Vlahos (12).

Throughout this time period, indications for inpatient admission included diagnoses such as intractable pain, intractable nausea, pulmonary compromise, vascular occlusion, and neurologic events. The general management strategy for inpatients included conservative IV rehydration with crystalloid until oral fluids were tolerated, correction of electrolyte imbalance as indicated, serial laboratory evaluation of hematologic and electrolyte indices, and deep venous thrombosis prophylaxis with antiembolism stockings, sequential compression devices, and/or SC heparin (when hematocrit was >50%). Intravenous antiemetics and pain medications were administered as needed. In cases of severe discomfort or pulmonary compromise in hospitalized patients, inpatient transabdominal paracentesis was performed.

Outpatient transvaginal paracentesis began to be performed as primary management of patients with OHSS in 2002. The management strategy for patients primarily given treatment with outpatient transvaginal paracentesis included diligent telephone contact between the patient and her providers after the diagnosis of OHSS. Patients were instructed to keep a diary of their daily weight, abdominal circumference, number of urinary voids, subjective volume of urination, and symptoms including abdominal discomfort, shortness of breath, and gastrointestinal complaints. Prompt notification of the providers was required if any symptoms worsened, new symptoms developed, or weight or urine output changed. Patients were scheduled for an immediate office visit with a provider if any changes suggested worsening OHSS; physical examination, laboratory studies, and transvaginal ultrasound examination were performed at that time.

Aggressive outpatient transvaginal paracentesis was undertaken for symptom control with no limits on the volume of fluid removed. The same operating room used for vaginal oocyte retrieval was used for transvaginal paracentesis. Patients received minimal IV sedation. With the patient in the dorsal lithotomy position the vagina was cleansed with povidone-iodine (Betadine). A No. 17 egg retrieval needle affixed to a vaginal ultrasound probe was attached to conventional tubing and connected to operating room wall suction. Wall suction pressure was set at 200 mm Hg. Under direct ultrasound visualization, the egg retrieval needle was directed into the posterior cul-de-sac, suction activated, and ascites fluid drained. Paracentesis was continued until ultrasound examination showed the pelvic fluid to be maximally drained while avoiding needle injury to adjacent bowel or other vital structures. The procedure generally required less than a half hour to complete, and patients remained in the outpatient surgery center for no longer than 3 hours. If the outpatient laboratories indicated hemoconcentration with a hematocrit >50%, outpatient anticoagulation with either SC heparin or enoxaparin sodium (Lovenox) was initiated.

All analyses of medical record data were conducted with use of Statistical Analysis System (SAS 9.1.3; SAS Institute, Cary, NC). Medians were compared with the Mann-Whitney U test, and P<.05 was considered statistically significant. The study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center.

RESULTS

From 1999 to 2007, 9,707 patients at our center underwent 20,538 fresh IVF cycles from a total of approximately 5,500 patients receiving treatment each year for infertility. During

this time period, 183 patients were identified with the diagnosis of OHSS. All patients were managed with inpatient hospitalization (with or without inpatient transabdominal paracentesis), outpatient transvaginal paracentesis, or expectant management without intervention. The mean age of patients with OHSS was 33.6 years (\pm SD: 4.4 years), most were otherwise healthy, and 16 (9%) had polycystic ovary syndrome. The majority (81%) of patients underwent cycles initiated and completed as IVF, 9.8% were from cycles initiated and completed as controlled ovarian hyperstimulation, and 9.2% were from cycles that were initiated as controlled ovarian hyperstimulation and converted to IVF because of exaggerated response. The median peak E₂ level was 2,364 pg/mL (range 228–8,261 pg/mL), and median number of oocytes retrieved was 15.0 (range 3–60).

In total, from 1999 to 2007, 45 of the 183 patients with OHSS (25%) were hospitalized, accounting for 177 days of inpatient care. The median hospital stay was 4.0 days (range 0-14 days). Thirteen of these 45 patients underwent inpatient transabdominal paracentesis because of intractable pain or pulmonary compromise. The mean volume of ascites fluid removed during inpatient transabdominal paracentesis was 1,917 mL (range 1,000-3,500 mL). Of these 13 total patients who underwent inpatient transabdominal paracentesis, 12 had severe OHSS (9 with grade 5 and 3 with grade 4) and 1 had moderate OHSS (grade 3) by the criteria of Whelan and Vlahos (12). In this 9-year period, 10 patients (5%) had serious and potentially life-threatening complications of OHSS including pulmonary emboli (2 patients), deep venous thrombosis (2 patients), pleural effusion requiring chest tube drainage (1 patient), stroke (1 patient), acute renal failure (2 patients), and transient hepatitis (2 patients).

In 2002, outpatient transvaginal paracentesis was initiated as the primary treatment modality for OHSS. Since 2002, a total of 146 outpatient transvaginal paracenteses have been performed to manage OHSS in 96 patients with no complications related to the procedure. The mean volume of ascites fluid removed was 2,155 mL (range 500–4,500 mL). Thirty-five patients (36%) underwent a second outpatient transvaginal paracentesis because of reaccumulation of ascites fluid, eight patients (8%) required a third, three patients (3%) required a fourth, and one patient (1%) required five outpatient transvaginal paracenteses.

Comparison of the number of patients requiring hospitalization before and after the initiation of aggressive outpatient transvaginal paracentesis in the treatment of OHSS demonstrates clinically significant differences. In the 3 years from 1999 through 2001, 29 patients required hospitalization for OHSS or complications related to OHSS compared with only 16 patients in the 6 years from 2002 to 2007. This is a dramatic decrease in the number of hospitalized patients, considering that the total number of patients treated for infertility at our center has remained stable over time. With the implementation of early, aggressive, outpatient transvaginal

FIGURE 1

Management of OHSS 1999 through 2007.



paracentesis, the number of patients requiring hospitalization for OHSS clearly has decreased (Fig. 1).

Analysis of inpatient management before and after the initiation of outpatient transvaginal paracentesis reveals further differences. Eleven of the 29 patients hospitalized from November 1999 through 2001 (38%) were treated with inpatient transabdominal paracentesis. In the 6 years since the start of aggressive outpatient transvaginal paracentesis in 2002, only 2 of the 16 hospitalized patients (13%) underwent transabdominal paracentesis. As seen in Table 1, the annual rates of hospitalization and inpatient paracentesis decreased markedly after the initiation of outpatient transvaginal paracentesis in 2002. Finally, the median hospital stay of 4.0 days (range 1-14 days) from 1999 to 2001 was statistically significantly longer than the median hospital stay of 2.0 days (range 0-9 days) after outpatient paracentesis became the primary treatment modality for OHSS in 2002 (P=.003), suggesting that the intervention of outpatient transvaginal paracentesis did not simply delay the hospitalization of patients who were ultimately sicker.

Interestingly, from 1999 through 2001 hospitalized patients routinely were given IV 5% albumin infusions in an attempt to expand intravascular volume and improve urine output. However, since then no hospitalized patients were administered albumin, and no patients who were treated solely with outpatient transvaginal paracentesis ever were given albumin.

Specific ART cycle characteristics before and after the initiation of aggressive outpatient transvaginal paracentesis in 2002 were analyzed, including median peak E_2 , number of oocytes retrieved, and number of embryos transferred in these two time periods. There was no statistically significant difference in median peak E_2 or number of oocytes retrieved.

TABLE	1					
Summary of interventions in IVF cycles complicated by OHSS.						
	Calculated per 1,000 cycles			Calculated per 1,000 patients		
Year	Hospitalizations	Inpatient paracenteses	Outpatient paracenteses	Hospitalizations	Inpatient paracenteses	Outpatient paracenteses
1999	3.96	0.44	0	5.72	0.64	0
2000	3.77	1.51	0	5.79	2.32	0
2001	2.93	2.09	0	4.22	3.02	0
2002	0.79	0.40	3.97	1.18	0.59	5.90
2003	0.78	0	5.82	1.16	0	8.72
2004	0.85	0	8.03	1.26	0	11.94
2005	0.94	0	7.98	1.37	0	11.64
2006	1.64	0.55	9.84	2.33	0.78	13.95
2007	1.11	0	5.00	1.66	0	7.46
Smith. OHSS transvaginal paracentesis. Fertil Steril 2009.						

The median peak E_2 level was 2,180 pg/mL before 2002 and 2,391 pg/mL after the initiation of transvaginal paracentesis (P=.83). The corresponding medians for the number of oocytes retrieved were 15.5 and 15.0 (P=.69). There was a statistically significant difference between the median number of embryos transferred before and after 2002. The median number of embryos transferred from 1999 to 2001 was 3.0 (range 2–4) compared with 2.0 (range 1–8) between 2002 and 2007 (P<.0001).

Even with the use of early, aggressive, outpatient transvaginal paracentesis as the primary treatment modality for OHSS, there has continued to be a small number of patients each year who require hospitalization. Of the 16 patients hospitalized with OHSS from 2002 to 2007, the primary indication for admission in 11 patients (69%) was intractable pain. Nine of these 16 patients had severe OHSS (four grade 5 and five grade 4), three had moderate OHSS (grade 3), and four had mild OHSS (grade 2). The five patients admitted with indications other than pain had the following diagnoses: [1] severe OHSS (grade 4), intractable nausea, and fulminant hepatitis (peak aspartate aminotransferase level 298 IU/L, peak alanine aminotransferase level 464 IU/L); [2] severe OHSS (grade 5) and a persistent right pleural effusion requiring thoracentesis (800 mL); [3] severe OHSS (grade 5) and an ischemic stroke requiring a prolonged intensive care unit stay; [4] severe OHSS (grade 5) and a pulmonary embolus; and [5] severe OHSS (grade 5), neck swelling, and right internal jugular thrombosis. These 16 patients required a total of 41 days of inpatient care.

To better understand our practice patterns, a standardized grade and stage was assigned to each patient with a diagnosis of OHSS. Although we were unable to access the full records to classify the OHSS grade and stage of all 183 patients in this series, information was obtained on all patients beginning in 2006. With use of the system proposed by Whelan and Vlahos, the 77 patients with OHSS since 2006 were categorized into mild, moderate, and severe stages with the accompanying grades of distinction (12). A total of 26 patients had mild OHSS (grade 1 or 2), 22 patients had moderate OHSS (grade 3), 18 patients had severe OHSS (grade 4), and 11 had severe OHSS (grade 5). Those with mild OHSS were managed entirely as outpatients with expectant management. Of the 51 patients with a diagnosis of moderate (grade 3) or severe (grade 4 or 5) OHSS, 46 (90%) were managed solely as outpatients with either expectant management alone or outpatient transvaginal paracentesis. Of these 51 patients, 29 had severe OHSS, and 25 (86%) of them were managed entirely as outpatients with no complications. From 2006 to 2007, 5 patients (10%) with moderate or severe OHSS required hospitalization.

Pregnancy outcome data were available for 176 patients. One hundred thirty-two patients (72%) were pregnant: 104 had confirmed pregnancies with fetal cardiac activity by first trimester ultrasound examination (55 singletons, 42 twins, 7 triplets), 15 initially had fetal cardiac activity on ultrasound examination but ultimately had a first-trimester miscarriage, 6 had biochemical pregnancies, and the pregnancy outcome was unknown for 7 patients. Of the 44 nonpregnant patients, 12 had all embryos cryopreserved, 4 had cycle cancellation (2 because no normal embryos were found on preimplantation genetic screening), and 7 were oocyte donors.

DISCUSSION

Ovarian hyperstimulation syndrome continues to be among the most serious complications of ovulation induction with exogenous gonadotropins. Because this complication of assisted reproductive therapy is both iatrogenic and possibly life threatening, Whelan and Vlahos (12) asserted that all physicians who prescribe medications with the potential to cause OHSS are obligated to know the risk factors, prevention strategies, staging, and treatment. The treatment algorithms for OHSS have centered historically on inpatient management of fluid status. There has been, however, a gradual movement in the literature toward increasing outpatient management of OHSS.

Paracentesis is the primary intervention that has been demonstrated to improve patient symptoms and improve objective measures of OHSS disease state. Paracentesis as part of the management of OHSS is not a new concept and was first suggested by Rabau et al. in 1967 (10). The physiologic basis behind the technique has its foundation in the gastrointestinal literature with the use of large-volume paracentesis in the management of patients with cirrhosis who were refractory to diuretics (24). Immediately after paracentesis, characteristic hemodynamic changes occur including decreased intraabdominal pressure, improved venous return, and improved renal perfusion. In patients with cirrhosis, the maximal hemodynamic effect was demonstrated after the removal of >750 mL of ascites fluid (25). In addition to the mechanical improvements in blood flow occurring after removal of ascites fluid and decreased intra-abdominal pressure, the other mechanism by which paracentesis has been proposed to improve condition in OHSS is by the direct removal of the inflammatory, vasodilatory, and angiogenic substances released by hyperstimulated ovaries (26, 27).

In the gynecologic literature, several groups have investigated the hemodynamic and renal effects of transabdominal paracentesis in patients with OHSS. Chen et al. (28) measured uterine and intraovarian artery pulsatility index, maximum peak systolic velocity, and 24-hour urine output before and after transabdominal paracentesis in seven pregnant patients with severe OHSS. They found a significant decrease in the mean pulsatility index of the uterine arteries and a significant increase in 24-hour urine output after transabdominal paracentesis and concluded that repeated abdominal paracentesis increases uterine perfusion without any early adverse obstetric outcomes in pregnant patients with severe OHSS (28). Maslovitz et al. (26) performed transabdominal paracentesis in 19 women with severe OHSS and measured urine output and renal artery blood flow by Doppler ultrasound. They found decreased renal artery resistance in patients undergoing paracentesis with a concomitant urine output increase of 65% by the day after the procedure and attributed these results to improved renal artery blood flow after decompression. Furthermore, in those patients who were identified to have oliguria before paracentesis, urine output increased by an astonishing 200% by the day after paracentesis (26). Levin et al. (29) showed a similar improvement in urine output and serum indicators of renal function and hemoconcentration in 30 patients with symptoms and severe OHSS treated with transabdominal paracentesis.

Despite these dramatic improvements in renal function demonstrated to follow paracentesis in patients with OHSS, many clinicians consider the indications for paracentesis to be limited to those patients with severe discomfort, severe pulmonary status, and severe renal compromise as a strategy to shorten hospital stay (12, 21, 30, 31). The abdominal approach has been described in the literature as being "favored" because of improved patient comfort and easier accessibility during the procedure, but several groups have demonstrated excellent results with transvaginal drainage of ascites (17). In 1990, Aboulghar et al. (32) evaluated the effectiveness of inpatient transvaginal paracentesis in 11 patients with severe OHSS and demonstrated shorter inpatient stay and immediate resolution of symptoms. These findings were confirmed by larger studies in patients with severe OHSS that again demonstrated shorter hospitalization and immediate alleviation of respiratory compromise and renal insufficiency after inpatient transvaginal paracentesis (21, 33).

There has been a further trend toward outpatient paracentesis in the management of OHSS with the goals of minimizing disease progression and potentially avoiding hospitalization altogether. In 1994, Shrivastav et al. (34) assigned 18 patients with severe OHSS to either a conservative management protocol with hospitalization or a more actively managed group who underwent early, outpatient, transabdominal paracentesis. They found that outpatient transabdominal paracentesis produced prompt symptom relief and effectively avoided inpatient care. Transvaginal paracentesis combined with IV administration of crystalloid and albumin also has been demonstrated to be a safe and effective strategy in the management of patients with moderate to severe OHSS (22, 23). Going even one step further, several reports have described the use of an indwelling transabdominal pigtail catheter placement for continuous drainage of ascites fluid in patients with OHSS, and one group reported the use of outpatient transabdominal percutaneous catheter drainage in patients with severe OHSS (35-37).

We report one of the largest series of patients with OHSS treated with outpatient transvaginal paracentesis. Of our 96 patients managed with outpatient transvaginal paracentesis, none had complications from the procedure. There were no ascending vaginal infections leading to intraperitoneal infection, a concern about the procedure that has been raised in the past (36). There were no cases of bowel injury during the procedure and no episodes of intra-abdominal hemorrhage caused by inadvertent puncture of massively enlarged and highly vascularized ovaries. With our increase in the use of outpatient transvaginal paracentesis in the management of patients with OHSS, we have observed a decrease in the number of patients requiring hospitalization for OHSS despite a stable number of patients undergoing treatment for infertility each year. We have demonstrated that outpatient transvaginal paracentesis may be used safely in the management of patients with even severe OHSS.

Admittedly, there are limitations in the use of a retrospective case series to make conclusions about outcomes after a change in clinical practice. The results shown here may be influenced by confounding variables for which adjustments are now impossible. The intensity of pharmacologic ovarian stimulation is one possible confounder, and one could argue that ovarian stimulation may have been more aggressive during the early years of the series and less aggressive during the later years of the series. This could lead to a decrease in the total number of patients in whom OHSS develops and account for the decrease in hospitalizations. However, no substantial changes in stimulation protocol were made during the period of this study. In general, agonist remained the primary stimulation method, although in latter years there was slightly more antagonist use. Likewise, there was no change in luteal management during the period of this study, with consistently >90% of patients receiving vaginal P. In an attempt to address this possible confounder, analysis of the median peak E2 and median number of oocytes retrieved from patients with OHSS may serve as a surrogate marker for intensity of stimulation. There was no statistically significant difference in the peak level of E2 or the number of oocytes retrieved before and after the initiation of aggressive outpatient transvaginal paracentesis.

The number of embryos replaced or the decision to cryopreserve all embryos in a cycle could be a confounding variable if the number of embryos replaced were higher in the early years of the series and the number of cycles in which all embryos were cryopreserved were higher in the later years of the series. The median number of embryos transferred in the years from 1999 to 2001 was 3.0, compared with 2.0 in the years from 2002 to 2007, but it is impossible to accurately compare the rate of triplets in 1999 to 2001 with that in 2002 to 2007 because of unstable estimates resulting from small sample size. It can be noted that despite a higher median number of embryos transferred earlier in the series, the total number of triplet pregnancies in this entire 9-year period was only 7. The pattern of triplet pregnancy is as follows: 1999–1; 2000-2; 2001-2; 2006-1; 2007-1. From 1999 to 2007, there were only 12 patients who had all embryos cryopreserved. These patients were equally distributed throughout the series. On the basis of these data, it cannot be argued that the lower incidence of hospitalization for OHSS in the second half of the series was due simply to a shift in practice pattern in number of embryos transferred.

Review of our experience with transvaginal paracentesis to treat patients with OHSS reveals an additional unique feature to our management algorithm: IV colloid never has been used for intravascular volume expansion in patients treated as outpatients, and no adverse consequences from this exclusion have been identified. There has been an ongoing debate as to the value of IV albumin as a preventative measure in OHSS. A recent randomized controlled study conclusively demonstrated that IV albumin infused at the time of vaginal oocyte retrieval in patients at high risk for the development of OHSS resulted in no difference in ultimate hospitalization, need for paracentesis for OHSS, or complications (38). Clearly, there is a difference between the use of albumin as a preventative measure to avoid the development of OHSS and the use of albumin in the acute setting of moderate or severe OHSS with its associated intravascular volume depletion and oliguria. Our experience shows that even in patients with severe OHSS, albumin therapy is not required to accompany transvaginal paracentesis, and the possible risks of using a product derived from human plasma are avoided entirely (23, 39).

It is critical to note, as others have in the past, that outpatient management of patients with OHSS requires extreme diligence on the part of both the patient and her providers (23). Our goal in this review of our management of patients with OHSS was not to state that OHSS is a benign process, which is treated entirely with a simple outpatient visit. Ten of our patients had potentially life-threatening complications of OHSS despite active and aggressive management. Rather, our goal in describing this case series was to show that although there will continue to be a small percentage of patients with OHSS who require inpatient care, the majority of patients can be managed safely and effectively with early outpatient transvaginal paracentesis and diligent outpatient follow-up. Furthermore, in our experience, even severe OHSS can be safely managed with outpatient transvaginal paracentesis, and prolonged inpatient hospitalization should no longer be a foregone conclusion.

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REFERENCES

- Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventative measures. Hum Reprod Update 2003;9:275–89.
- Tollan A, Holst N, Forsdahl F, Fadnes HO, Oian P, Maltau JM. Transcapillary fluid dynamics during ovarian stimulation for in vitro fertilization. Am J Obstet Gynecol 1990;162:554–8.
- Goldsman MP, Pedram A, Dominguez CE, Ciuffardi I, Levin E, Asch RH. Increased capillary permeability induced by human follicular fluid: a hypothesis for an ovarian origin of the hyperstimulation syndrome [see comments]. Fertil Steril 1995;64:871–2.
- Paul M, Mehr AP, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev 2006;86:747–803.
- Lightman A, Tarlatzis BC, Rzasa PJ, Culler MD, Caride VJ, Negro-Vilar AF, et al. The ovarian renin-angiotensin system: renin-like activity and angiotensin II/III immunoreactivity in gonadotropin-stimulated and unstimulated follicular fluid. Am J Obstet Gynecol 1987;156: 808–16.
- Wang T-H, Horng S-G, Chang C-L, Wu H-M, Tsai Y-J, Wang H-S, et al. Human chorionic gonadotropin–induced ovarian hyperstimulation syndrome is associated with up-regulation of vascular endothelial growth factor. J Clin Endocrinol Metab 2002;87:3300–8.
- Pau E, Alonso-Muriel I, Gomez R, Novella E, Ruiz A, Garcia-Velasco JA, et al. Plasma levels of soluble vascular endothelial growth factor receptor-1 may determine the onset of early and late ovarian hyperstimulation syndrome. Hum Reprod 2006;21:1453–60.
- Chen C-D, Chen H-F, Lu H-F, Chen S-U, Ho H-N, Yang Y-S. Value of serum and follicular fluid cytokine profile in the prediction of moderate to severe ovarian hyperstimulation syndrome. Hum Reprod 2000;15: 1037–42.
- Abramov Y, Schenker JG, Lewin A, Friedler S, Nisman B, Barak V. Plasma inflammatory cytokines correlate to the ovarian hyperstimulation syndrome. Hum Reprod 1996;11:1381–6.
- Rabau E, David A, Serr DM, Mashiach S, Lunenfeld B. Human menopausal gonadotropin for anovulation and sterility. Am J Obstet Gynecol 1967;98:92–8.

- Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an updated review. Obstet Gynecol Surv 1989;44:430–40.
- Whelan JG, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril 2000;73:883–96.
- Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome: a review. Hum Reprod Update 2002;8:559–77.
- Rizk B, Aboulghar M. Modern management of ovarian hyperstimulation syndrome. Hum Reprod 1991;6:1082–7.
- Brinsden PR, Wada I, Tan SL, Balen A, Jacobs HS. Diagnosis, prevention, and management of ovarian hyperstimulation syndrome. Br J Obstet Gynecol 1995;102:767–72.
- 16. Klemetti R, Sevon T, Gissler M, Hemminki E. Complications of IVF and ovulation induction. Hum Reprod 2005;20:3293–300.
- Delvigne A, Rozenberg S. Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Hum Reprod Update 2003;9:77–96.
- Morris RS, Miller C, Jacobs L, Miller K. Conservative management of ovarian hyperstimulation syndrome. J Reprod Med 1995;40:711–4.
- Vlahos NF, Gregoriou O. Prevention and management of ovarian hyperstimulation syndrome. Ann NY Acad Sci 2006;1092:247–64.
- Padilla SL, Zamaria S, Baramki TA, Garcia JE. Abdominal paracentesis for the ovarian hyperstimulation syndrome with severe pulmonary compromise. Fertil Steril 1990;58:249–61.
- Aboulghar MA, Mansour RT, Serour GI, Sattar MA, Amin YM, Elattar I. Management of severe ovarian hyperstimulation syndrome by ascitic fluid aspiration and intensive intravenous fluid therapy. Obstet Gynecol 1993;81:108–11.
- 22. Lincoln SR, Opsahl MS, Blauer KL, Black SH, Schulman JD. Aggressive outpatient treatment of ovarian hyperstimulation syndrome with ascites using transvaginal culdocentesis and intravenous albumin minimizes hospitalization. J Assist Reprod Genet 2002;19:159–63.
- Fluker MR, Copeland JE, Yuzpe AA. An ounce of prevention: outpatient management of the ovarian hyperstimulation syndrome. Fertil Steril 2000;73:821–4.
- Forouzandeh B, Konicek F, Sheagren JN. Large-volume paracentesis in the treatment of cirrhotic patients with refractory ascites: the role of postparacentesis volume expansion. J Clin Gastroenterol 1996;22:207–10.
- 25. Cabrera J, Falcon L, Gorriz E, Pardo MD, Granados R, Quinones A, et al. Abdominal decompression plays a major role in early post paracentesis hemodynamic changes in cirrhotic patients with tense ascites. Gut 2001;48:384–9.
- Maslovitz S, Jaffa A, Eytan O, Wolman I, Many A, Lessing JB, et al. Renal blood flow alteration after paracentesis in women with ovarian hyperstimulation. Obstet Gynecol 2004;104:321–6.

- Delbaere A, Bergmann PJ, Gervy-Decoster C, Staroukine M, Englert Y. Angiotensin II immunoreactivity is elevated in ascites during severe ovarian hyperstimulation syndrome: implications for pathophysiology and clinical management. Fertil Steril 1994;62:731–7.
- Chen C-D, Yang J-H, Chao K-H, Chen S-U, Ho H-N, Yang Y-S. Effects of repeated abdominal paracentesis on uterine and intraovarian haemodynamics and pregnancy outcome in severe ovarian hyperstimulation syndrome. Hum Reprod 1998;13:2077–81.
- Levin I, Pharm B, Almog B, Avni A, Baram A, Lessing JB, et al. Effect of paracentesis of ascitic fluids on urinary output and blood indices in patients with severe ovarian hyperstimulation syndrome. Fertil Steril 2002;77:986–8.
- 30. Raziel A, Friedler S, Schachter M, Strassburger D, Bukovsky I, Ron-El R. Transvaginal drainage of ascites as an alternative to abdominal paracentesis in patients with severe ovarian hyperstimulation syndrome, obesity, and generalized edema. Fertil Steril 1998;69:780–3.
- American Society for Reproductive Medicine Practice Committee educational bulletin: ovarian hyperstimulation syndrome. Fertil Steril 2006;86:S178–83.
- Aboulghar MA, Mansour RT, Serour GI, Amin Y. Ultrasonically guided vaginal aspiration of ascites in the treatment of ovarian hyperstimulation syndrome. Fertil Steril 1990;53:933–5.
- Abramov Y, Elchalal U, Schenker JG. Pulmonary manifestations of severe ovarian hyperstimulation syndrome: a multicenter study. Fertil Steril 1999;71:645–51.
- Shrivastav P, Nadkarni P, Craft I. Day care management of severe ovarian hyperstimulation syndrome avoids hospitalization and morbidity. Hum Reprod 1994;9:812–24.
- Al-Ramahi M, Leader A, Claman P, Spence J. Case report: a novel approach to the treatment of ascites associated with ovarian hyperstimulation syndrome. Hum Reprod 1997;12:2614–6.
- Abuzeid MI, Nassar Z, Massaad Z, Weiss M, Ashraf M, Fakih M. Pigtail catheter for the treatment of ascites associated with ovarian hyperstimulation syndrome. Hum Reprod 2003;18:370–3.
- Chan CC, Yin CS, Lan SC, Chen IC, Wu GJ. Continuous abdominal paracentesis for management of late type severe ovarian hyperstimulation syndrome. J Chin Med Assoc 2004;67:197–9.
- Bellver J, Munoz EA, Ballesteros A, Soares SR, Bosch E, Simon C, et al. Intravenous albumin does not prevent moderate-severe ovarian hyperstimulation syndrome in high-risk IVF patients: a randomized controlled study. Hum Reprod 2003;18:2283–8.
- Gokmen O, Ugur M, Ekin M, Keles G, Turan C, Oral H. Intravenous albumin versus hydroxyethyl starch for the prevention of ovarian hyperstimulation in an in vitro fertilization programme: a prospective, randomized, placebo controlled study. Eur J Obstet Gynecol Reprod Biol 2001;96:187–92.