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Aggressive Outpatient Treatment of Ovarian Hyperstimulation Syndrome With Ascites Using Transvaginal Culdocentesis and Intravenous Albumin Minimizes Hospitalization[1]

Stephen R. Lincoln,[2,3] Michael S. Opsahl,[2] Keith L. Blauer,[2] Susan H. Black,[2] and Joseph D. Schulman[2]

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***Purpose*:** To assess the effectiveness of outpatient treatment of Ovarian Hyperstimulation Syndrome associated with ascites.

***Methods*:** Forty-eight patients diagnosed with ovarian hyperstimulation and ascites from 2246 consecutive in vitro fertilization cycles were retrospectively studied. Patients were treated with outpatient transvaginal culdocentesis and rehydration with intravenous crystalloids and albumin every 1–3 days until resolution of symptoms or hospitalization was required. Outcomes measured included incidences of hospitalization, pregnancy outcomes, cycle characteristics, and oocyte donors versus nondonors comparisons.

***Results*:** No complications occurred from outpatient treatments, and 91.6% of patients avoided hospitalization. The pregnancy rate in patients undergoing transfer was 84.7%, and the spontaneous loss rate was 16%. Overall, the estradiol on day of hCG was 4331 pg/mL (range 2211–8167), ascites removed was 1910 cm^3 (122–4000), and number of outpatient treatments was 3.4 (1–14). Nondonors averaged more outpatient treatments than donors (3.97 vs. 1.85), but similar rates of hospitalization (3/35 vs. 1/13).

***Conclusions*:** Outpatient treatment consisting of culdocentesis, intravenous rehydration, and albumin minimized the need for hospitalization in hyperstimulated patients.

KEY WORDS: Albumin; culdocentesis; ovarian hyperstimulation syndrome.

INTRODUCTION

Ovarian Hyperstimulation Syndrome (OHSS) is a potentially lethal iatrogenic complication of ovulation induction with gonadotropin therapy. The incidence of severe OHSS is estimated to be between 0.5 and 1.8% (1–3). Severe OHSS is characterized by an increased capillary permeability resulting in a transudate fluid shift out of the intravascular compartment into third space compartments (4,5). Severe disease can be associated with ovarian enlargement, massive ascites, hydrothorax, hemoconcentration, electrolyte imbalance, hypovolemia, oliguria, and thromboembolic phenomenon (2,3,6). Severe clinical manifestations may include acute renal insufficiency, adult respiratory distress syndrome, liver dysfunction, and even death (7).

Treatment of severe OHSS includes bed rest, oral balanced salt solutions, intravenous fluid therapy, and removal of ascites (7–10) in an effort to prevent critical end organ failure associated with renal shutdown

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[2] Genetics and IVF Institute, 3020 Javier Road, Fairfax, Virginia 22031.

[3] To whom correspondence should be addressed.

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and adult respiratory distress syndrome. Treatment with intravenous therapy and removal of ascites usually takes place in the hospital setting. The primary purpose of this study is to assess the safety and efficacy of aggressive outpatient treatment of OHSS associated with ascites in patients undergoing in vitro fertilization (IVF). In addition, pregnancy outcomes in those patients electing to proceed with embryo transfer were reviewed. Finally, characteristics of OHSS oocyte donors and infertile patients were compared.

MATERIALS AND METHODS

The medical records of 48 women treated with outpatient transvaginal culdocentesis were identified from 2246 consecutive cycles of IVF. Inclusion criteria included the presence of abdominal ascites on ultrasound and clinical symptoms of shortness of breath, abdominal distention, or discomfort. All patients were felt to be classified as moderate to severe OHSS as described by the Golan Classification System (11). All patients were treated in a single large private practice infertility center.

Outpatient treatment consisted of office visits every 1–3 days until resolution of symptoms. After confirming the presence of abdominal ascites, an ultrasound guided transvaginal culdocentesis was performed through the posterior culdesac in a fashion similar to an oocyte retrieval for IVF. Patients received a vaginal betadine prep before the procedure and usually oral doxycycline afterwards. Light intravenous conscious sedation resulted in little or no patient discomfort during all procedures. All patients were rehydrated with intravenous crystalloid solutions and albumin beginning before the procedure and continuing afterwards until equal amounts of fluid were replaced as were removed during the culdocentesis. Intravenous albumin (25–50 g) was diluted in crystalloids (50–1000 cm^3) to approximate a 5% albumin solution.

Outcome data included the incidence of OHSS, number of patients with successful outpatient treatment versus patients who required hospitalization, and pregnancy outcomes after embryo transfer. In addition, characteristics of OHSS patients were detailed including the number of follicles and estradiol level on the day of hCG administration, number of days to first outpatient treatment, amount of ascites removed at culdocentesis, and number of outpatient visits. Finally, comparisons were made between oocyte donor and infertility patients. Of the 48 patients, 13 were donors and 35 were IVF patients.

Statistical analysis was performed using SPSS statistical software (Version 10, Chicago, IL) for the data comparison of oocyte donors and infertility patients. Parametric data (including age, number of follicles, and volume of ascites removed) was analyzed by way of ANOVA. The data from number of days until culdocentesis and number of outpatient treatment was not normally distributed, and therefore these nonparametric data were analyzed by the Krushel–Wallis test. P values <0.05 were considered statistically significant.

RESULTS

The incidence of OHSS requiring treatment was 2.1% (48/2246) in our study population. The incidence of OHSS in donor patients (2.0%–13/650) was not different from infertility patients (2.2%–35/1596). Table I summarizes the rate of successful outpatient treatments as well as the pregnancy outcome data. Outpatient treatment of OHSS was successful in over 90% of patients, and no complications directly attributable to the outpatient culdocentesis occurred. Infertile patients elected to proceed with transfer in 31 of 35 cases. Patients undergoing fresh embryo transfer who developed OHSS had a high pregnancy rate (26/31–84%). The OHSS patients electing to freeze all embryos appear to have good outcomes with all patients conceiving from one of their frozen embryo transfers (4/4–100%). Early pregnancy loss (16%) appears no different than the general obstetrical population. Twenty-five live births occurred including 13 singletons, 9 sets of twins, 2 sets of triplets, and 1 set of quadruplets. The average number of embryos transferred per patient was 3.3.

The characteristics of OHSS patients are summarized in Table II. The average age was 30.3 years, and

Table I. Hospitalization Rate and Pregnancy Data

Incidence of OHSS	48/2246 (2.1%)
No. of patients avoiding hospitalization (successful outpatient treatment)	44/48 (91.6%)
No. of patients hospitalized (failed outpatient treatment)	4/48 (8.3%)
No. of OHSS patients pregnant	26/31[a] (84%)
Spontaneous abortions or blighted ovum	5/30[b] (16.6%)

[a] 31 of 35 nondonor patients elected to proceed with fresh embryo transfers.
[b] 30 pregnancies includes the four patients who froze all embryos at the time of the fresh cycle and conceived during a frozen cycle.

Table II. Characteristics of OHSS Patients

Age (year)	30.31 ± 0.59 (22–39)
Estradiol on day of hCG (pg/mL)	4331.33 ± 194.76 (2211–8167)
No. of follicles ≥12 mm at hCG	24.85 ± 1.34 (9–55)
Days from hCG to culdocentesis	9.25 ± 0.64 (3–20)
Fluid removed at culdocentesis (cm^3)	1910.13 ± 59.21 (122–4000)
No. of outpatient treatments/patient	3.40 ± 0.45 (1–14)

Note. Values expressed as mean, SEM, and range.

the average serum estradiol on the day of hCG was 4331 pg/mL with a wide range of values (2211–8167). As expected, the number of follicles ≥12 mm on the day of hCG was also large [25] with a wide range (9–55). The time from hCG to culdocentesis averaged just over 9 days, and the amount of fluid removed on average was 1910 cm^3 (range 120–4000 cm^3). Patients averaged 3.4 outpatient visits before resolution of symptoms.

Since the majority of infertile patients underwent embryo transfer and none of the oocyte donors did so, comparisons of the course of OHSS in these two groups were made (Table III). Oocyte donor patients on average were younger (27.4 vs. 31.4 years), but had similar levels of estradiol at the time of hCG. Although statistically not significant, oocyte donors tended to make more follicles ≥12 mm (28.46 vs. 23.51), but have less ascites removed at each culdocentesis (1634 vs. 1957 cm^3). Infertile patients averaged more days from the time of hCG to the first culdocentesis (10.4 vs. 6.23 days) and had more outpatient visits (3.97 vs. 1.85). Although the numbers were small, donor and infertile patients had similar rates of hospitalization (7.7% vs. 8.6%).

DISCUSSION

We report one of the largest series of patients with OHSS in the literature, and this study is the first to describe treatment in the outpatient setting. In his recent literature review (12), Whalen described OHSS as a serious and life-threatening iatrogenic complication of gonadotropin therapy. He urged all physicians using gonadotropin to understand the pathophysiology, apply preventative measures when appropriate, and to know the treatment regimens for OHSS. The exact pathogenesis of OHSS is still unclear, but one or more potential inciting factors found in ascites have been described. Angiotensin II is a product of the ovarian renin–angiotensin system that may increase vascular permeability and is elevated in ascites from OHSS (13,14). More recently, vascular endothelial growth factor (VEGF) has been implicated as a primary candidate for inducing OHSS (15,16). The glycoprotein VEGF stimulates endothelial cell proliferation, permeability, and angiogenesis. It is our hypothesis that removal of some of these factors found in ascites with replacement of fluid may reduce the severity and progression of OHSS.

Treatment regimens for OHSS described in the literature and elsewhere usually include hospitalization. Patient treatment in this study consisted predominantly of transvaginal culdocentesis and intravenous rehydration with crystalloid solutions and albumin. In addition, patients were encouraged to drink electrolyte-balanced solutions as tolerated and limited strenuous activity, but not bed-rest. Removal of ascites fluid by aspiration has generally been shown to be helpful in treating OHSS (7,10,21). The effectiveness of albumin in the prevention and treatment of OHSS is more controversial. Our purpose was not to debate the validity of these treatments, but to show they could be performed safely in an outpatient setting.

Table III. Comparisons of Donor vs. Nondonor Patient With OHSS

No. of patients	Donor ($n = 13$)	Nondonor ($n = 35$)	P value
Age (years)[a]	27.38 ± 0.87 (23–33)	31.40 ± 0.65 (22–39)	0.002[b]
Estradiol at hCG[a]	4260.54 ± 252.02 (2872–6095)	4357.63 ± 252.00 (2211–8167)	0.95[c]
No. of follicles ≥12 mm at hCG[a]	28.46 ± 2.87 (17–55)	23.51 ± 1.46 (9–44)	0.102[b]
Days from hCG to 1st culdocentesis[a]	6.23 ± 0.51 (3–9)	10.37 ± 0.78 (4–20)	0.004[c]
Fluid removed at culdocentesis[a]	1633.67 ± 152.96 (500–3000)	1957.87 ± 63.56 (122–4000)	0.052[c]
No. of outpatient treatments/patient	1.85 (1–5)	3.97 ± 0.58 (1–14)	0.24[c]
Hospitalization rate	1/13 (7.7%)	3/35 (8.6%)	

[a] Values expressed as mean, SEM, and range.
[b] Pairwise comparisons for parametric data.
[c] Kruskal–Wallis test for nonparametric data.

The debate over the use of albumin in OHSS centers on both prevention and treatment. Asch and colleagues first reported prophylactic administration of albumin prevented OHSS in 36 high risk patients (18). Shoham *et al*. (10) described a similar benefit in a small random prospective study where 16 high risk OHSS patients received albumin and did not develop severe OHSS, whereas a control group (no albumin) had 4/15 develop severe OHSS. Follow-up studies have shown mixed results with no benefit of prophylactic albumin reported by some authors (17,19), while others continue to describe reduction of OHSS (20).

Although the vast majority of our patients would meet the definition of severe OHSS (11), some were started on treatment before they developed hemoconcentration, electrolyte imbalances, or renal function abnormalities. However, all patients who met the criteria of clinically significant ascites by ultrasound and symptoms including shortness of breath, severe distention, and abdominal discomfort were treated. We believe that early aggressive outpatient treatment aids in preventing life-threatening complications and waiting for laboratory results would not change management of these patients. In our series, no patient developed critical end stage OHSS as others have reported, including thromboemolic phenomenon, end stage renal disease, acute respiratory distress syndrome, myocardial infarction, or cardiovascular compromise requiring a Dopamine drip.

Outpatient treatment versus hospitalization offers several advantages, not the least of which is cost savings. We have found performing culdocentesis in our IVF retrieval rooms easier than in the hospital where assembling the necessary equipment can be cumbersome. This report confirms the safety and effectiveness of outpatient treatment. However, four of our patients did eventually require hospitalization necessitating continuous abdominal paracentesis by way of a temporary abdominal drain and in one case a thorocentesis was done. Hospitalization occurred when repetitive culdocenteses for massive ascites (2000–4000) removal transpired on a continuous daily basis. One patient underwent 12 outpatient treatments before finally agreeing to admission during the 12th procedure. The tap was immediately stopped after removing only 122 cm^3 of fluid to allow better visualization for ultrasound-guided placement of a permanent continuous abdominal drain. Hospitalization varied between 4 and 8 days for all patients. We believe early outpatient treatment with the onset of significant ascites lowers the risk of severe complications of OHSS, but more studies in other centers are needed to confirm our observations.

The pregnancy data in our study revealed two encouraging trends. Patients who become pregnant and have OHSS do not seem at increased risk of early pregnancy loss. Second, patients who elect to forego fresh embryo transfer and cryopreserved all embryos appear to have good pregnancy rates with the frozen embryo transfers. If this trend continues we can further reassure patients who choose to forego fresh embryo transfer when at risk of severe OHSS.

We compared donor versus infertile patients to see if any differences in the course of OHSS could be found. Our infertile patients required twice as many outpatient treatments and had a longer duration of illness. Infertile patients also tended to have more ascites removed but this finding did not reach statistical significance. These observations are most likely due to the majority of infertile patients becoming pregnant with endogenous production of hCG and prolonged stimulation of multiple follicles. In addition, donor patients were continued on down regulation with GnRH-Antagonist (Lupron 20 units s.c.) for 7 days after retrieval. With a successful cryopreservation program, cryopreservation of all embryos in patients at risk for OHSS may become standard of care.

CONCLUSION

In summary, aggressive outpatient treatment with culdocentesis and intravenous rehydration including albumin minimized the need for hospitalization for patients with OHSS and ascites. Pregnancy rates are extraordinarily high in such patients. Adverse pregnancy outcomes appear no different than the general obstetrical population. Infertile patients develop OHSS later and require more outpatient treatments than oocyte donor patients, probably due to the large number of infertile patients who conceive.

REFERENCES

1. Medical Research International, Society for Assisted Reproductive Technology (SART), The American Fertility Society: In vitro fertilization-embryo transfer (IVF-ET) in the United States: 1990 results from the IVF-ET Registry. Fertil Steril 1992;57:15–24
2. Schenker JG, Weinstin D: Ovarian hyperstimulation syndrome: A current survey. Fertil Steril 1978;30:255
3. Sroitz J, Camus M, Devrorcy P, Beard P, Wisanto A, Van Steirteghem AC: Incidence of severe ovarian hyperstimulation

syndrome after GnRH agonist/HMG superovulation for in-vitro fertilization. Hum Reprod 1990;5:933–937
4. 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;162:554–558
5. 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 comment]. Fertil Steril 1995;63:268–272
6. Borenstein R, Elhalah U, Lunenfeld B, Schwartz ZS: Severe ovarian hyperstimulation syndrome: A reevaluated therapeutic approach. Fertil Steril 1989;51:791–795
7. 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;81:108–111
8. Navot D, Bergh PA, Laufer N: Ovarian hyperstimulation syndrome in novel reproductive technologies: Prevention and treatment. Fertil Steril 1992;58:249–261
9. 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;69:780–783
10. Shoham Z, Weissman A, Barash A, Borenstein R, Schachter M, Insler V: Intravenous albumin for the prevention of severe ovarian hyperstimulation syndrome in an in vitro fertilization program: A prospective, randomized, placebo-controlled study. Fertil Steril 1994;62:137–142
11. Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E: Ovarian hyperstimulation syndrome: An update review. Obstet Gynecol Surv 1989;44:430–440
12. Whelan JG, Vlahos NF: The ovarian hyperstimulation syndrome. Fertil Steril 2000;73:883–896
13. Navot D, Margalioth EJ, Laufer N, Birkenfeld A, Relou A, Rosler A, Schenker JG: Direct correlation between plasma renin activity and severity of the ovarian hyperstimulation syndrome. Fertil Steril 1987;48–57
14. Delbaere A, Bergmann P, Gervy-Deroster C, Deschodt-Lanckman M, de Maertelaer V, Staroukine M, Camus M, Englert Y: Increased angiotensin II in ascites during severe ovarian hyperstimulation syndrome: Role of early pregnancy and ovarian gonadotropin stimulation. Fertil Steril 1997;67: 1038–1045
15. Levin ER, Rosen GF, Cassidente DL, Yee B, Meldrum D, Wisot A, Pedram A: Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. J Clin Invest 1998;102:1978–1985
16. Agrawal R, Tan SL, Wild S, Sladkevicius P, Engman L, Payne N, *et al.*: Serum vascular endothelial growth factor concentrations in in vitro fertilization cycles predict the risk of ovarian hyperstimulation syndrome. Fertil Steril 1999;71:287–293
17. Isik AZ, Gokmen O, Zeyneloglu HB, Kara S, Keles G, Gulekli B: Intravenous albumin prevents moderate-severe hyperstimulation in in-vitro fertilization patients: A prospective, randomized and controlled study. Eur J Obstet Gynecol Reprod Biol 1996;70:179–183
18. Asch RH, Ivery G, Goldsman M, Fredrick JL, Stone SC, Balmaceda JP: The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. Hum Reprod 1993;8:1015–1020
19. Chen CD, Wu MY, Yang JH, Chen SU, Ho HN, Yang YS: Intravenous albumin does not prevent the development of severe ovarian hyperstimulation syndrome. Fertil Steril 1997;68:287–291
20. Isik AZ, Vicdan K, Alaybeyouglu L: Does IV Albumin prevent severe ovarian hyperstimulation? [Letters to the Editor]. Fertil Steril 1998;69:356–357
21. Aboulghar MA, Mansour RT, Serour GI, Amin Y: Ultrasonically guided vaginal aspiration of ascites in the treatment of severe ovarian hyperstimulation syndrome. Fertil Steril 1990;53:933–935