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Medical Journal of Obstetrics and Gynecology

Research Article

Use of Mannitol Therapy for Ovarian Hyperstimulation Syndrome (OHSS) Management

AboTaleb Saremi*, Maryam NamdarKhanzadeh, Maryam Shami, Fariba Mohammad Aliha, and Arash Pooladi

Sarem Fertility & Infertility Research Center (SAFIR), Sarem Women's Hospital, Iran

***Corresponding authors**

AboTaleb Saremi, Sarem Women's Hospital, End of Phase 3, ShahrakEkbatan, Tehran, 1396956111, Iran, Tel: 989121213234; 98 21 44670888 ; Fax: 98 21 44670432 ; Email: saremiat@yahoo.com

Submitted: 31 October 2016

Accepted: 29 January 2017

Published: 01 February 2017

ISSN: 2333-6439

Keywords

- Ovarian hyperstimulation syndrome
- OHSS
- Management
- Mannitol therapy

Abstract

Background and aims: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially fatal complication of assisted reproductive technologies (ART) that occurs due to an acute fluid shift from the intravascular space to the third space. Based on the disease pathophysiology and the mechanism of the effects of mannitol, in this report we propose it as an effective medical choice to manage the signs and symptoms of OHSS. This study was designed to evaluate the efficacy of mannitol therapy in the management of OHSS.

Materials and methods: Data were collected through interventional non-experimental daily practice in an IVF (In vitro fertilization) department treating patients with moderate and severe OHSS (based on the Rizk&Aboulghar classification) over a period of nearly 8 years, from April 2008to February 2016, in the Sarem Women's Hospital. To design a protocol for mannitol administration in OHSS, approved doses and methods under definite conditions (intracranial pressure, intraocular pressure) were considered. Mannitol therapy was started daily or twice a day, and the dose of mannitol was adjusted between 1 and 1.5 g/kg/dose according to clinical signs and their severity. Patients were monitored according to the standard protocols. All clinical data were collected and analyzed by SPSS version 23 software.

Results: Of 5227 women who entered the ovarian stimulation protocol for IVF over a period of 8 years, 1205 developed OHSS (23.05%). The frequency of mild, moderate, and severe types was seen in 918 (76.18%), 254

921.08%), and 33 (2.74%) patients, respectively.Only clinically important types (moderate and severe cases) received medical intervention (287 patients). Weight loss after mannitol therapy ($P = 0.0159$), the difference in the mean fluid intake/urine output (I/O) before vs. after treatment (-349.60 ± 1289.81 vs. 641.80 ± 1032.54 ($P = 0.0048$), the decrease in the mean duration of hospitalization to 4.72 ± 2.92 days, and the 0.0% mortality rate were the major outcomes of our suggested protocol. The cost of mannitol used in OHSS management is approximately 1/30 to 1/25 of the cost of albumin. No IVF cycles were cancelled in our OHSS patients.

Conclusion: The results of our study showed that the effects of mannitol therapy on controlling the signs and symptoms of OHSS, the major indices of patient improvement, and the mortality and morbidity rates were acceptable. Due to the low cost of mannitol, fewer bed occupancy days, and no IVF cycle cancelation, managing OHSS with mannitol is remarkably cost-efficient.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially fatal complication of assisted reproductive technologies (ART) that can occur following controlled ovarian hyperstimulation (COH) after the administration of human chorionic gonadotropin (hCG) [1]. OHSS may develop early or late after exposure to hCG. Early OHSS occurs immediately after oocyte retrieval and reflects the effect of exogenous hCG, which is administered to achieve final follicular maturation following the excessive ovarian response to follicle-stimulating hormone (FSH). Late OHSS occurs 10 days or more after the ovulatory dose of hCG and is caused by endogenous hCG produced by the primary pregnancy; it may be more severe and more dangerous than the early form, and it is difficult to predict [2]. Whereas mild OHSS is of no clinical significance and does not require intervention, its severe form is difficult to control and treat, and is a life-threatening complication [3,4]. OHSS presents with the enlargement of the ovaries, ascites, hydrothorax, electrolyte

disturbance, hypovolemia, and oliguria [1]. As a result of an acute fluid shift from the intravascular space to the third space [mainly the abdominal and thoracic cavities), the fluid accumulates in the peritoneal cavity and the pleura, hematocrit rises, and organ perfusion decreases. The symptoms of the syndrome vary from bloating to a feeling of lung fullness and dyspnea [5]. The ovaries show significant stromal edema with multiple hemorrhagic follicular and theca-lutein cysts, necrosis of the cortex, and revascularization. It is believed that the fluid shift results from an increase in the capillary permeability [3,4,6,7].

The prevalence of severe and moderate OHSS is reported to be 0.1% to 2% and 3% to 6% in the literature, respectively, but the prevalence increases to 38% or more in women in the high-risk group [1,2,8], which highlights the importance of detecting high-risk patients and adopting preventive measures in this group of patients. However, the risk of OHSS is always inherent, even in non-high-risk women [3]. Although prevention is the better strategy for the control of OHSS, the treatment and case management strategies for OHSS patients require focus, too. There have been a few non-effective (or questionable) choices for medical or nonmedical options for the treatment of OHSS [3, 8-14]. For example, albumin was the drug of choice for OHSS management [15] when we started the study. Although albumin has been classically used to prevent and treat OHSS, its efficacy is a matter of controversy [16-19]. However, albumin was expensive and not always available in Iran (due to an embargo); therefore, based on the pathophysiology of OHSS and the pharmacologic properties of mannitol, it was used as a replacement for albumin. Mannitol is a sugar alcohol [20], that works as an osmotic diuretic [21]. It causes osmotic diuresis by increasing the osmotic pressure in the glomerular filtrate and preventing water and electrolyte re-absorption. Infusion of mannitol is approved for controlling increased intracranial pressure in brain edema, increased intraocular pressure (IOP), and the stimulation of the urinary excretion of certain toxins [21].

Despite all of the significant advances in understanding the pathophysiology of OHSS, there is lack of information, and for this reason, OHSS prevention is the key approach for preventing OHSS-related morbidity and mortality [22, 23]. Thus, we describe the management approach of OHSS with mannitol to investigate the effect of this drug on controlling OHSS.

MATERIALS AND METHODS

Study design and patient selection

The study was performed over a period of nearly 8 years, from April 2008 to February 2016, in the Sarem Women's Hospital. The data were collected and analyzed using descriptive and analytical methods with SPSS version 23.

Due to the war, economic sanctions, and drug shortages, clinicians in the Sarem Medical Center had to replace albumin, which was expensive and difficult to find, with mannitol for a limited time because of its pharmacological properties.

To design a protocol for mannitol administration in OHSS, approved doses and methods in specific conditions (intracranial pressure (ICP), IOP) were followed [21]. For a comprehensive and credible administration method, the authors presented the primary satisfactory results of a compulsory primary pilot as evidence to the ethics committee of the medical center. After necessary evaluations and considering the safety of mannitol in the administered dose, the committee approved trying mannitol therapy for severe forms of OHSS on the conditions of observing the approved protocols and obtaining informed consent from the participants (approval number 3263-04, approval date: May 19, 1995). After that, based on the 1-year pilot study of mannitol and the safety of this drug, the research group continued the use of mannitol for the management of OHSS. The data from the ensuing 20 years had been collected, but because of ovarian induction protocol changes, only the most recent 8 years' data are used in this study. In this study all of the women were stimulated by the step-up and antagonist protocol especially in the high risk (e.g. PCOS) patients.

As mild OHSS requires no intervention [8,23], only patients with moderate and severe OHSS were included in the study. During the preparation of the patients for the IVF process and after ovarian stimulation, ultrasonic monitoring of the ovaries was performed in the infertility department. If a patient had the signs of moderate or severe OHSS despite prevention [8], she was entered into the study.

Patient monitoring and mannitol properties

During the treatment with mannitol, certain laboratory parameters and vital signs were evaluated, and clinical examinations were performed. The results were recorded in data registry forms on a daily basis to investigate the trend of the response to treatment, the complications of OHSS, and the side effects of mannitol.

The side effects of mannitol were closely monitored, and contraindications and warnings were considered. According to the medical literature, mannitol should not be used unless sufficient renal function and adequate urinary flow are ensured. It is suggested to evaluate the response of the kidneys after one or two doses. Careful clinical monitoring and evaluation of the drug dose during infusion, electrolyte control and correction (if necessary), and maintaining a serum osmolality less than 300 to 320 mOsm/kg are also recommended to minimize the side effects of the drug. Higher concentrations of mannitol; administering more than 200 g of mannitol per day; serum osmolality greater than 320 mOsm/kg or an osmolal gap greater than 50 mOsm/kg; concomitant use of other nephrotoxic drugs; sepsis; and underlying renal diseases increase the possibility of tubular necrosis or damage [21]. Moreover, mannitol infusion may result in electrolyte imbalance, dehydration, hypovolemia secondary to rapid diuresis, hyperglycemia, hypernatremia, hyponatremia, hyperosmolality-related hyperkalemia, metabolic acidosis, increased osmolar gap, and water intoxication [21]. These side effects, especially when overlapping with OHSS complications, demand more careful monitoring and follow-up. If patients experienced dyspnea, tachycardia, severe sweating, decreased output, or muscle cramps during mannitol therapy, a reduction in the dose of mannitol was considered. In patients receiving mannitol twice a day, we reduced the dose to once a day; in patients receiving one daily dose of mannitol, doses were withheld. To assess the risk of embolization in OHSS patients, plasma D-dimer measurement was added to the laboratory

tests in the final year of the study so that we could decide to prescribe heparin as prophylaxis if applicable. D-dimer testing was performed only on the first day of treatment after mannitol infusion. Serum osmolality measurements were also added to the monitoring parameters in the final months of the study.

Diuresis usually occurs 1 to 3 hours after mannitol infusion. The elimination half-life of mannitol is 4.7 hours. It has insignificant hepatic metabolism (to glycogen), and a urinary excretion of approximately 55% to 87% of the unchanged drug is recorded. Its distribution in the extracellular space is limited except in very high serum concentrations, and it cannot cross the blood-brain barrier [21].

The protocol of intravenous mannitol use

According to the Practice Committee of the American Society for Reproductive Medicine, the first priority in the management of OHSS is to correct hypovolemia, hypotension, and oliguria. (Note that all the patients with moderate and severe OHSS had a urinary catheter during mannitol therapy.) The committee recommends rapid hydration with intravenous fluids (500-1000 mL dextrose 5% and/or 0.9% saline) and careful monitoring of fluid intake during treatment to achieve adequate urine output (≥20-30 mL/h) and reverse hemoconcentration. Moreover, the guideline recommends 5% dextrose in normal saline (D5NS) rather than lactated Ringer's solution, given the tendency of the latter to cause hyponatremia. The guideline points to mannitol as a plasma expander as well as albumin and fresh frozen plasma for the fluid management of OHSS patients [15].

1- Considering the dose of mannitol in increased ICP, in IOP, and in cerebral edema, the mannitol therapy protocol was designed as folloMannitol therapy with 500-mL mannitol 20% was started once daily or twice daily (equal to 100-200 g mannitol per day, based on the severity of the patient's symptoms). The dose of mannitol was adjusted between 1-1.5 g/kg/dose according to clinical signs and their severity (ICP: 0.25-1 g/kg/dose, and IOP: 0.25-2 g/kg/dose [28]).

2- Each 500-mL mannitol 20% was infused with 500-mL D5NS solution through a Y-site over 4 hours to achieve the desirable initial 1000-mL dosRoutine abdominal examination, pulmonary auscultation, abdominal circumference measurement, and evaluation of diuresis and hemoconcentration were performed for decision making on the continuation of fluid therapy and, if indicated, after 4 hours of infusion, 500-mL D5NS was infused over 30-60 minutes. The second infusion was not performed if examinations indicated progressive fluid retention in the body [21].

3- During the infusion, attention was paid to maintaining an adequate level of urine output (≥ 20-30 mL/h); mannitol therapy was continued until abdominal and pulmonary signs were completely resolved. One of the improvement indices in the management of OHSS is that the total fluid output exceeds the total fluid intake, which indicates termination of fluid retention. This trend (output>intake) should be carefully monitored and recorded to make sure that the complications of OHSS are controlled. If in a 24-hour period the total fluid output was not more than the total fluid intake, the patient was placed on NPO (nil per os, or nothing by mouth), and mannitol was administered twice daily along with 500 mL of D5NS solution followed by an infusion of 1000 mL of solution after each dose of mannitol. The type of solution was selected based on the clinical considerations explained in clinical notes 1 and 2, which follow. Once the output was greater than the intake, NPO was discontinued and the patient received mannitol as before on a daily basis.

Clinical note 1: In patients with diabetes, normal saline (0.9% saline) was used instead of D5NS.

Clinical note 2: According to the patient's serum sodium (Na) level, dextrose 5% or half saline was used instead of D5NS to correct hypernatremia.

RESULTS

Of the 5227 women who entered the ovarian stimulation protocol for IVF over a period of 8 years from 2008 to 2016, there were 1205 OHSS cases (23.05%). Of these cases, 918 patients with mild OHSS comprised 76.18% of the total cases of OHSS and 17.56% of all induction cases. Moreover, 254 patients (21.08% of the OHSS cases and 4.86% of all the induction cases) and 33 patients (2.74% of the OHSS cases and 0.63% of all the induction cases) had moderate and severe OHSS, respectively. Among patients with severe OHSS, types A, B, and C were observed in 28 (2.32% of the OHSS cases), four (0.33% of the OHSS cases), and one (0.083% of the OHSS cases) patients, respectively. In total, 287 patients (moderate and severe cases, or 23.8% of all the OHSS cases) were clinically important and received medical intervention (Table 1).

The pregnancy rate (based on positive β-hCG) among patients with different severities of OHSS was 13.1% (158 patients). No significant relationship was observed between the occurrence of pregnancy and the severity of OHSS (x^2 = 3.025, df = 2, P value = 0.224), as pregnancy was observed in 14.05% (129 patients), 10.24% (26 patients), and 9.09% (3 patients) of those women with mild, moderate, and severe OHSS, respectively. There was no significant correlation between body mass index (BMI) and the severity of OHSS (ANOVA F = 0.915, df = 2, P value = 0.522). The clinical pregnancy rate (based on gestational sac detection), was 12.6% in OHSS patients (13.5%, 9.4%, and 9.1% for mild, moderate, and severe OHSS, respectively) - (Table 2).

Approximately 66.7% of the patients with severe OHSS had a primary diagnosis of various types of polycystic ovarian disease (PCOD) that was significantly correlated with the severity of OHSS (x^2 = 17.42, df = 2, P value = 0.0002), as 37.8% and 32.8% of the patients with moderate and mild OHSS had a primary diagnosis of PCOD, respectively. The same was true for the history of PCOD because 48.5%, 29.9%, and 21.35% of the patients with severe, moderate, and mild OHSS had a previous diagnosis of PCOD, respectively (x^2 = 19.31, df = 2, P value <0.0001). Of all of the patients with OHSS, 284 (23.6%) had a previous diagnosis of PCOD (Table 2).

Among the cases of secondary infertility, we found no significant relationship between the number of previous

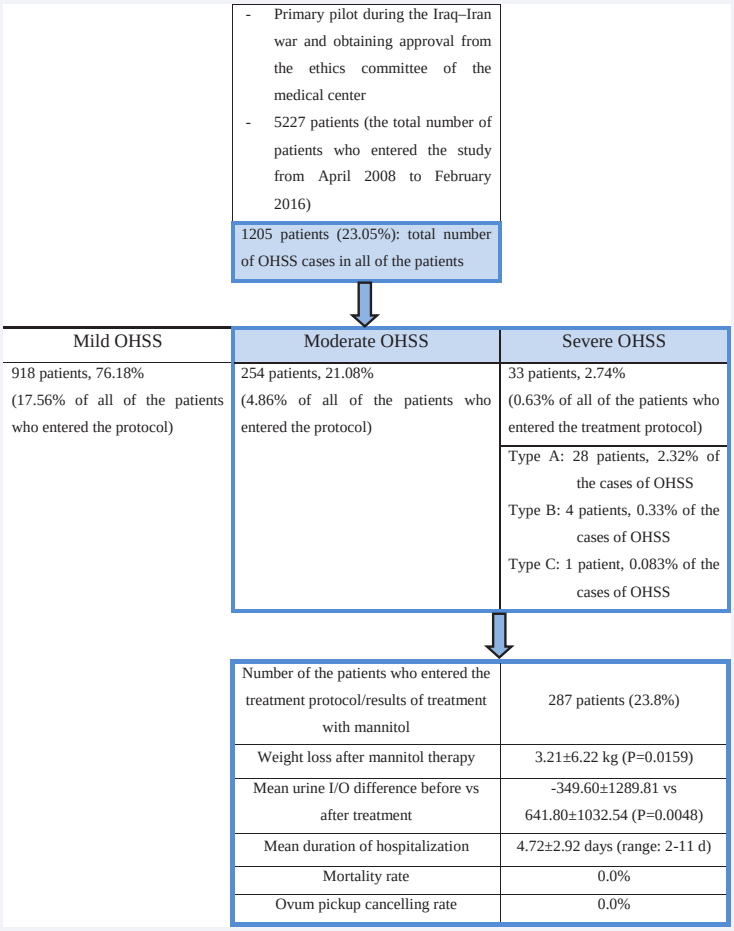

Table 1 The frequency of the study patients and the results of treatment using the mannitol protocol.

Table 2: Pregnancy rates and history of PCOD in OHSS groups.

OHSS Group	Number of Patients	Chemical Pregnancy Rate (Freq.)	Clinical Pregnancy Rate	History of PCOD*
Mild	918	14.05(129)	13.5	48.5
Moderate	254	10.24 (26)	9.4	29.9
Severe	33	9.09 (3)	9.1	21.35
Total	1205	13.1 (58)	12.6	-

pregnancies or deliveries and the severity of OHSS (P<0.05).

In this study, the analyses of the outcome of treatment with Mannitol were performed on cases with moderate and severe OHSS. The mean age of these patients was 29.66 ± 4.27 years. Embryo transfer was cancelled in 260 patients (90.6%) with moderate and severe OHSS (4.97% of all OHSS cases). The mean number of follicles that are ≥ 14 mm in diameter in patients with moderate and severe OHSS was 16.65 ± 5.46. The mean number of transferred embryos in patients with moderate and severe OHSS, in whose embryo transfers were not cancelled, was 2.57 ± 0.53 (Table 3).

After mannitol therapy, the following results were obtained on comparing patients with moderate and severe OHSS before and after treatment. The mean weight loss after mannitol therapy

Table 3: Clinical Outcomes for Moderate and Severe OHSS under Mannitol therapy.

Clinical Outcomes for Moderate and Severe OHSS	Percentage (Freq.) Or Mean (SD)
Embryo Transfer Cancellation	90.6 (260)
No. of Follicle ≥14 mm	16.65 (5.46)
No. of Transferred Embryo	2.57 (0.53)
Mean Weight Loss (Kg) *	3.21 (6.22)
Mean D-Dimer level	0.51 (0.438)
Mean Osmolar Gap (mOsmol/kg)	13.76 (11.1)
*** P-value<0.05**	

(weight on admission day – weight on discharge day) was 3.21 ± 6.22 kg, which was significantly different compared with weights before the treatment (paired t-test, t = -2.425, df = 285, P-value = 0.0159). The mean D-dimer of the patients was 0.51 ± 0.438 mg/L, and the mean osmolar gap in these 63 patients was 13.76 ± 11.1 mOsmol/kg (range: 0.17-41.54) during treatment (Table 3).

Among all 287 patients, 27.9% had oliguria (<0.5 mL/kg/h), (4.2% had severe oliguria, <0.1 mL/kg/h), and the remaining patients had an adequate urine output. After treatment, the rate was reduced to 17.4% for oliguria (1.4% had severe oliguria), which was significantly different (P<0.05). The mean 24-hour urinary intake/output difference was -349.60 ± 1289.81 mL in the patients before treatment, and increased to 641.80 ± 1032.54 mL after treatment, indicating a significant difference (paired t-test, t = -2.843, df = 285, P-value = 0.0048). Correction of the hemoconcentration was observed after mannitol therapy, but it was not statistically significant (P>0.05)- (Table 4).

No mortality occurred in patients on Mannitol therapy during the study period.Two patients developed severe complications due to OHSS, because of the failure in their care to follow the mannitol therapy protocol. The first case was a 36-year-old woman with primary infertility. The signs of moderate-to-severe OHSS were observed after ovarian stimulation in this patient, and she had inadequate urinary output. The protocol was not observed in this patient, and the patient received more than the maximum dose of mannitol (5000 mg/kg/day). She also received 1400 g mannitol for 7 days, which should not have exceeded 100 g. This patient was hemodialyzed once and recovered after 3 days of hospitalization. Pregnancy did not occur in this patient. The second case was a 24-year-old woman with primary infertility who was placed on mannitol therapy despite oliguria and received approximately 1300 g of mannitol in 8 days (13 doses), which was again more than the maximum allowable dose defined in our protocol.

Another major outcome of the mannitol therapy was a mean patient hospitalization period of 4.72 ± 2.92 days (range: 2-11 d). It should be noted that 12 and 7 patients with severe OHSS had abdominal discomfort and respiratory distress before treatment, respectively, which resolved with mannitol therapy.

DISCUSSION

Although the precise pathophysiologic pathways of OHSS are unclear, some seem to be more important. Increased vascular permeability is caused by vasoactive substances that are produced by hyperstimulated ovaries, with vascular endothelial growth factor (VEGF) being the most important [2,3,5]. The role of VEGF in the pathogenesis of OHSS has been widely investigated by researchers [5,24-28]. According to in vitro studies, hCG is a strong stimulator of ovarian granulosa cells for the secretion of vascular endothelial growth factor (VEGF), which can explain the clinical relationship between hCG and OHSS [2,5]. VEGF plays a major role in increasing the capillary permeability in OHSS-related ascites [5,8]. In addition, the role of inflammation-related cytokines and interleukins [10,24], inhibin A and B, selectins (like E-selectin), the von Willebrand factor, immunoglobulin changes, metabolic changes [8], and the renin-angiotensin system in the development and severity of OHSS has been demonstrated [29,30]. It is not clear whether mannitol can interact or bind with any of these factors, especially VEGF, to manifest its efficacy besides its osmotic diuresis and volume expansion. More investigations are needed to understand these molecular mechanisms.

Table 4: Clinical Outcomes for Moderate and Severe OHSS; comparison between before and after Mannitol therapy.

Clinical outcomes for Moderate and Severe OHSS	Before Treatment: Percentage (Freq.) Or Mean (SD)	After Treatment: Percentage (Freq.) Or Mean (SD)
Oliguria (<0.5 mL/kg/h)*	27.9 (80)	17.4 (50)
Severe Oliguria (<0.1 mL/kg/h)*	4.2 (12)	1.4 (4)
Mean 24-hour Urinary Intake/Output Difference (ml)*	-349.6 (1289.8)	+641.8 (1032.54)
* P-value<0.05		

The molecular structure, mechanism of action, contraindications, precautions, and recommended dosage of mannitol administration were all considered in the protocol design for the management of OHSS. Mannitol is very hydrophilic due to the presence of numerous alcoholic groups (-OH) in its molecular structure. The molecules of water bind to each mannitol molecule through hydrogen bonds and cause its osmotic-diuretic properties.

In our study, the incidence of mild, moderate, and severe OHSS in patients was slightly less than those previously reported [1,2]. Weight gain, discomfort, and respiratory distress, as the indices of OHSS, improved significantly after treatment. The correction of oliguria or anuria and the urine intake/output trends were significant after treatment. The diuretic effect of mannitol and adequate diuresis indicate achievement of the treatment objectives. Concerning the fact that there was no significant correction of the hemoconcentration, it should be noted that in a constant volume of red blood cells, the change in hematocrit is never numerically commensurate with the change in plasma volume, and the change in the plasma volume is of greater clinical relevance than the change reflected by hematocrit. In other words, an increase of 2 units in hematocrit from 45% to 47% is four times less than the actual 8% decrease in plasma volume and the severity of the disease. Similarly, even small decreases in hematocrit level during treatment may indicate significant improvements in plasma volume and the overall condition of the patient [8]. It is very important to pay attention to this issue during patient monitoring.

The mean D-dimer level was within the normal range in all of our patients. The mean and maximum osmolality and the mean and maximum osmolal gap during mannitol therapy confirmed the safety of the dose of mannitol in the designed protocol and indicated no mannitol accumulation in the intravascular space.

The mean duration of hospitalization in our study population was significantly shorter than previously reported in albumin therapy. A considerable decrease in costs as a result of the decrease in inpatient bed occupancy and the much lower cost of mannitol compared to albumin or hydroxyethyl starch was

another advantage of this protocol in the management of OHSS. In additionally, not canceling IVF cycles prevents abortive costs. Considering the high number of patients with moderate-to-severe OHSS in our study (377 patients), the lack of mortality and only two cases of morbidity were additional favorable results of this protocol.

There were some changes that are necessary for better and more reliable results for our recent study. Compare to our previous experiment, the difference of the current study are; Usage of the unique induction protocol especially for the high-risk (e.g. PCOS) patients (so more reliable statistics for OHSS prevalence were given and the treatment effects were conducted in the same condition for all patients in the view of the induction method), D-Dimer check in the patients (whereas We had not used the Heparin in our patients routinely, because of the low level of D-Dimer) and Non-use of Paracentesis in patients (So, the risk of infections was reduced and loss of albumin was not occurs) [31]. It must be mentioned that, the lack of the control group in this study is the major limitation of the study that can be followed by a RCT study for confirmation of the Mannitol therapy efficacy.

CONCLUSION

The results of our study showed the benefits of mannitol in the management of OHSS. According to our findings, the effects of mannitol therapy on controlling the signs and symptoms of OHSS, the major indices of patient improvement, and the mortality and morbidity rates are acceptable. In additional, mannitol therapy is tremendously effective at saving money for the health system. Finally, we suggest further randomized controlled studies to compare the efficacy of mannitol with other available methods and medications in the management of OHSS. For this reason a RCT study is undertaken by our research group in this field.

ACKNOWLEDGMENTS

The authors wish to thank all colleagues at the supporting institutes: Sarem Women's Hospital and Sarem Fertility and Infertility Research Center (SAFIR). Special thanks to Mrs. Leila Zand Azad, Mrs. NooshinFarahbakhsh, and Mrs. FaezehMoalemGhamsari for helping us gather data.

REFERENCES

1. Aboulghar M. Symposium: Update on prediction and management of OHSS. Prevention of OHSS. Reproduct biomed online. 2009; 19: 33-42.
2. Prakash A, Mathur R. Ovarian Hyperstimulation Syndrom. The Obstetrician & Gynecologist. 2013; 15: 31-35.
3. Matorras R, Andres M, Mendoza R, Prieto B, Pijoan JI, Exposito A. Prevention of ovarian hyperstimulation syndrome in GnRH agonist IVF cycles in moderate risk patients: randomized study comparing hydroxyethyl starch versus cabergoline and hydroxyethyl starch. Eur J Obstet Gynecol Reprod Biol. 2013; 170: 439-443.
4. Aboulghar MA, Mansour RT, Serour GI. Ovarian Hyperstimulation syndrome: modern consepts in patho-physiology and management. East Fertil Soc J. 1996; 1: 3-16.
5. Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2012; 2: CD008605.
6. Schrenker J, Weinsten D. Ovarian Hyperstimulation syndrome: a current survey. fertility and sterility. 1978; 30: 255-268.
7. Tollan A, Holst N, Forsdahl F, Fadnes HO, Oian P, Maltau JM. Transcapillary fluid dynamics during overian stimulationfor in vitro fertilization. Am J Obstet Gynecol. 1990; 162.
8. Brinsden PR. Textbook of in vitro fertilization and assisted reroduction: informa healthcare. 2007. 688.
9. Saremi A, Alam M, Motaghi M. Administration of mannitol to prevent severe ovarian hyperstimulation syndrome : A randomized controlled trial. Mid Fertil Socie J. 2003; 8: 159-163.
10. Chen C, Chen H, Lu H, Chen S, Ho H, YS Y. Value of serum and follicular fluid cytokine profile in the prediction of moderate to severe ovarian hyperstimulation syndrome. Hum Reprod. 2000; 15: 1037-1042.
11. Asch RH, Ivery G, Goldsman M, Frederick JL, Stone SC, Balmaceda JP. Clinical Report: The use of intravenous albumin in patients at high risk for severe ovarian hyperstimulation syndrome. Hum Reprod. 1993; 8: 1015-1020.
12. Shalev E, Giladi Y, Matilsky M, Ben-Ami M. Decreased incidence of severe ovarian hyperstimulation syndrome in high risk in-vitro fertilization patients receiving intravenous albumin: a prospective study. Human Reproduction. 1995; 10:1373-1386.
13. Isik AZ, Gokmen O, Zeyneloglu HB, Kara S, Keles G, Gulekli B. Intravenous albumin prevents moderate-severe ovarian hyperstimulation in in-vitro fertilization patients: a prospective, randomized and controlled study. Eur J Obstet Gynecol Reprod Biol. 1996; 70: 179-183.
14. Kissler S, Neidhardt B, Siebzehnrubl E, Schmitt H, Tschaikowsky K, Wildt L. The detrimental role of colloidal volume substitutes in severe ovarian hyperstimulation syndrome: a case report. Eur J Obstet Gynecol Reprod Biol. 2001; 9: 131-134.
15. Practice Committee of American Society for Reproductive M. Ovarian hyperstimulation syndrome. Fertil Steril. 2008; 90: S188-193.
16. 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: 2283-2288.
17. Venetis CA, Kolibianakis EM, Toulis KA, Goulis DG, Papadimas I, Tarlatzis BC. Intravenous albumin administration for the prevention of severe ovarian hyperstimulation syndrome: a systematic review and metaanalysis. Fertil Steril. 2011; 95: 188-196.
18. An SJ, Jee BC, Suh CS, Kim SH, Choi YM, Moon SY. Administration of intravenous albumin around the time of oocyte retrieval to prevent ovarian hyperstimulation syndrome: a meta-analysis. fertility and sterility. 2008; 90: S244-S245.
19. Youssef MA, Al-Inany HG, Evers JL, Aboulghar M. Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011: CD001302.
20. Kearsley MW, Deis RC. Sorbitol and Mannitol Sweeteners and Suger Altervatives in Food Technology: Blackwell publishing Ltd. 2006; 249-261.
21. American Pharmacist Associaton A. Drug Infomation Handbook. Ohio: Lexicomp inc. 2012; 2387.
22. Gao MZ, Zhao XM, Sun ZG, Hong Y, Zhao LW, Zhang HQ. Endocrine gland-derived vascular endothelial growth factor concentrations in follicular fluid and serum may predict ovarian hyperstimulation syndrome in women undergoing controlled ovarian hyperstimulation. Fertil Steril. 2011; 95: 673-678.
23. Aboulghar M. Treatment of ovarian hyperstimulation syndrome.

Seminars in reproductive medicine. 2010; 28: 532-539.

24. Rizk B, Aboulghar M, Smitz J, Ron-El R. The role of vascular endothelial growth factor and interleukins in the pathogenesis of severe ovarian hyperstimulation syndrome. Hum Reprod Update. 1997; 3: 255-266.

25. Levin ER, Rosen GF, Cassidenti DL, Yee B, Meldrum D, Wisot A, et al. Role of vascular endothelial cell growth factor in Ovarian Hyperstimulation Syndrome. J Clin Invest. 1998; 102: 1978-1985.

26. Shweiki D, Itin A, Neufeld G, Gitay-Goren H, Keshet E. Patterns of expression of vascular endothelial growth factor (VEGF) and VEGF receptors in mice suggest a role in hormonally regulated angiogenesis. J Clin Invest. 1993; 91: 2235-2243.

27. Agrawal R, Conway GS, Sladkevicius P, Payne NN, Bekir J, Campbell S, et al. Serum vascular endothelial growth factor (VEGF) in the normal menstrual cycle: association with changes in ovarian and uterine Doppler blood flow. Clin Endocrinol. 1999; 50: 101-106.

28. McClure N, Healy DL, Rogers PA, Sullivan J, Beaton L, Haning RV, et al. Vascular endothelial growth factor as capillary permeability agent in ovarian hyperstimulation syndrome. Lancet. 1994; 344: 235-236.

29. Navot D, Margalioth EJ, Laufer N, Birkenfeld A, Relou A, Rosler A, et al. Direct correlation between plasma renin activity and severity of the ovarian hyperstimulation syndrome. Fertil Steril. 1987; 48: 57-61.

30. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet. 2010; 27: 121-128.

31. Saremi A, Namdar khanzadeh M, Shami M, Alaiha F, Pooladi A. The Efficacy of Mannitol Therapy in the Management of Moderate and Severe Forms of Ovarian Hyperstimulation Syndrome: A New Application. Sare J M. 2012; 1: 9-19.

Cite this article

Saremi AT, Khanzadeh MN, Shami M, Aliha FM, Pooladi A (2017) Use of Mannitol Therapy for Ovarian Hyperstimulation Syndrome (OHSS) Management. Med J Obstet Gynecol 5(1): 1093.