Ovarian Hyper-Stimulation Syndrome during Intracytoplasmic Sperm Injection procedure for Infertile Polycystic Ovary patients could be a Preventable Tragedy

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Abstract: Objectives: To evaluate and compare the preventive efficacy and safety of bromocriptine tablets and calcium infusion on the frequency and severity of ovarian hyper-stimulation syndrome (OHSS) in polycystic ovary syndrome (PCOS) women assigned for intracytoplasmic sperm injection (ICSI). **Patients & Methods:** The current retro-prospective included 30 PCOS women (Group A) completed their ICSI program according to the protocol assigned for the prospective part of the study and developed OHSS and 60 patients randomly divided into 2 equal groups: Group B received bromocriptine 2.5 mg/day started on day of ovum pickup for 16 days and Group C included 30 patients received intravenous 10% calcium gluconate 10 ml in 200 ml saline on the day of ovum pickup and on days 1, 2 and 3 after ovum pickup. Ovarian stimulation program using gonadotrophine releasing hormone (GnRH)-agonist was started at the luteal phase and when at least two follicles had reached a diameter of ≥18 mm, rFSH was stopped, and a single subcutaneous bolus of 10,000 IU hCG was administered 36 hrs before the planned time of oocyte retrieval. The ICSI procedure was performed and a maximum of two embryos were transferred 3days after egg retrieval. Luteal support in the form of intravaginal progesterone was given daily from the day of oocyte retrieval for 16 days and was continued for up to12 weeks if pregnancy occurred. Outcome was defined as the frequency and severity of OHSS. **Results:** Ten patients (16.7%) in prospective part developed OHSS; 7 had mild and 3 patients had moderate manifestations with non-significant difference between both study groups as regards the frequency of OHSS and that of moderate OHSS. On contrary; 13 patients (43.3%) in the retrospective part developed OHSS with significantly higher frequency compared to the prospective part, irrespective to preventive therapy. Among those had OHSS in the retrospective part; 7 had mild and 5 had moderate manifestation and one patient developed severe manifestations necessitated hospitalization; an event that dose not occur in the prospective part. Concerning severity, there was significantly higher frequency of high severity grades among patients of the retrospective versus the prospective part of the study. **Conclusion:** Prevention of OHSS in PCOS women committing ART is feasible and safe provided proper patient selection was followed. The non-significant difference between both modalities of OHSS prevention as regards clinical pregnancy rate and both the frequency and severity of OHSS opened the way for patients' preference of the preventive modality and their general health status to be the selection guide.

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1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most concerning complication of controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART). It is a broad spectrum of signs and symptoms that include abdominal distention and discomfort, enlarged ovaries, ascites and other complications of enhanced vascular permeability, **(Rajesh *et al.*, 2011; Wiwanitkit, 2011)**.

There are many well-known and clearly-documented risk factors for the development of OHSS including: young age, low body mass index (BMI), polycystic ovarian syndrome (PCOS), allergic history, high antral follicle count, high doses of gonadotropins, high or rapidly rising estradiol levels, large numbers of large and medium-sized follicles, large numbers of eggs retrieved, high or repeated doses of hCG, pregnancy, and prior OHSS **(Kumar *et al.*, 2011; Lamazou *et al.*, 2011)**.

The syndrome is characterized by cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neo-angiogenesis. The possible contributing factors in the pathophysiology of OHSS are increased secretion of exudation of protein-rich fluid from enlarged ovaries or peritoneal surfaces. Molecules in the renin-angiotensin system which is widely known to regulate fluid balance; increased follicular fluid levels of prorenin and rennin and increased angiotensin-mediated changes in capillary permeability are among the first systems investigated as a potential contributor to the findings in OHSS. Vascular

endothelial growth factor (VEGF) which is a vasoactive glycoprotein that stimulates endothelial cell proliferation, cell permeability, and angiogenesis have been implicated in the pathophysiology of OHSS. Other possible mechanisms for the development of OHSS have been suggested, including FSH receptor variability **(Kumar *et al.*, 2011; Lamazou *et al.*, 2011)**.

Rennin secretion from juxtaglomerular cells is positively regulated by the second messenger cAMP and is inversely related to the extracellular and intracellular calcium concentration. Decreased intracellular calcium has stimulatory effect on adenylyl cyclase resulting in increased synthesis of cAMP and consequently rennin release. Thus calcium could indirectly modify rennin secretion which is responsible for angiotensin-mediated capillary permeability and increased vascular endothelial growth factor which is a potent stimulator of the vascular endothelium and plays an integral role in the follicular growth, corpus luteum function and ovarian angiogenesis **(Ortiz-Capisano *et al.*, 2007, Soares *et al.*, 2008, Beierwaltes *et al.*, 2010)**.

Multiple policies were tried for prevention or amelioration of severity of OHSS in women prepared for assisted reproduction technology (ART); through cycle canceling, modification of the ovulation triggering agents, coasting **(Garcia-Velasco *et al.*, 2004)** or administration of macromolecules as hydroxyethyl starch **(Konig *et al.*, 1998)** or albumin **(Bellver *et al.*, 2003)** or drug therapies using insulin-sensitizing agents **(Costello *et al.*, 2006)**, dopamine agonists, **(Carizza *et al.*, 2008)** or non-steroidal anti-inflammatory drugs **(Varnagy *et al.*, 2010)**.

Thus, the present study aimed to evaluate and compare the preventive efficacy and safety of bromocriptine tablets versus calcium infusion on the frequency and severity of OHSS in PCOS women assigned for ICSI.

2. Patients and Methods

The current single-blinded retro-prospective comparative study was conducted in the Assisted Reproductive Technologies Unit, Benha University Hospital and in private IVF centers between April 2010 and Jan 2012. The study protocol was approved by the Local Ethics Committee and written informed consents were obtained before the study commenced. The retrospective part included 30 PCOS women (Group A) completed their IVF or ICSI program according to the protocol assigned for the prospective part of the study and their files were found to include the complete data required for comparison versus the prospective part of the study; one of authors was blinded about these data. The prospective part included 60 women with PCOS assigned for ICSI procedure for different indications and were at risk of OHSS. The clinical enrollment data of women in the prospective part, showed non-significant difference compared to those chosen for the retrospective part.

The inclusion criteria were; [1] an age less than 35 years; [2] PCOS was diagnosed depending on the Rotterdam criteria, in which at least two of the following three criteria were met: oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenemia (serum total testosterone level >0.8 ng/ml), and polycystic ovaries (>12 follicles in the 2–9 mm range and/or an ovarian volume >10 ml per ovary by vaginal ultrasound) **(Rotterdam PCOS Consensus Workshop Group, 2004)**; [3] the presence of at least 20 pre ovulatory follicles in both ovaries, the majority being (12–14 mm in the mean diameter) and [4] serum estradiol (E2) level ≥ 3000 pg/ml. Exclusion criteria were: [1] endocrinopathies; [2] bronchial Asthma; [3] risk factors of or current cardiovascular diseases in which IV calcium is contraindicated; and [4] using any medication (e.g., GnRH antagonists and insulin-sensitizing drugs).

All women underwent controlled ovarian hyperstimulation (COH) with luteal phase GnRH-agonist long down regulation protocol. Long term desensitization protocol was done with GnRH agonist subcutaneously using Triptorelin acetate 0.1 daily (Decapeptyl GynTM; Ferring, Kiel, Germany) starting from day 21 of cycle preceding stimulating one. Adequate pituitary desensitization was established on 2nd or 3rd day of the menstrual cycle with the following criteria: thin endometrium, no follicular activity or cysts >1 cm and E2 level <50 pg/ml. Ovarian stimulation with gonadotropins was commenced on day 3 of the next cycle using recombinant-FSH (r-hFSH, Gonal-F®, 75 UI, Serono, Switzerland) at a daily dose 75-150 IU for the first 5-7 days. Dose adjustment depended on the individual response to treatment. Transvaginal ultrasound using 7-10 MHZ probe (Voluson 730 PRO V, GE Healthcare, USA) was done every 3-5 days for the examination of follicular development, and serum estradiol levels were measured every 2-3 days using radioimmunoassay method.

When the inclusion criteria were achieved ,patients in the prospective part of the study were randomly, using sealed envelops, divided into two equal groups: Group B received bromocriptine 2.5 mg **(Vlahos & Gregoriou, 2006)**, (Lactodel; bromocriptine mesylate, 2.87 mg equivalent to bromocriptine 2.5 mg; Amoun Pharmaceutical Co., El-Obour City, Cairo, Egypt). Treatment was started on the day of ovum pickup as a daily dose for 16 days. Group C included 30 patients assigned to receive intravenous 10% calcium gluconate as described by **Yakovenko *et al.*(2009)**, 10 ml in 200

ml physiological saline on the day of ovum pickup and on days 1, 2 and 3 after ovum pickup. Intravenous calcium infusion was conducted throughout 30 minutes.

When at least two follicles had reached a diameter of ≥18 mm and, rFSH was stopped, and a single intramuscular injection of 10,000 IU hCG (Choriomon®, IBSA, Switzerland) was administered 36 hrs before the planned time of oocyte retrieval, **(Huisman *et al.*, 2000)**. Subsequently, ICSI was performed, and a maximum of two embryos were transferred 72 hours thereafter, as described previously by **Huisman *et al.* (2000)**. All embryos were scored on the day of embryo transfer for developmental stage and morphology, using the described criteria by **Steer *et al.*(1992)** and good quality embryos were transferred. A good-quality embryo was defined embryo in G1 and G2 grade, having four blastomeres on day 2 or ≥8 blastomeres on day 3, less than 20% fragmentation, and no multinuclear blastomeres **(Steer *et al.*, 1992)**.

Luteal phase support (LPS) was started the day after ovum pick up by the vaginal administration of progesterone (Prontogest® 200 mg suppositories. Nile Company, Pharmaceuticals, Egypt) thrice daily for 16 days and was continued for up to12 weeks if pregnancy occurred.

Primary outcome was defined as the frequency and severity of OHSS according to the criteria by **Delvigne & Rozenberg (2002)**, as follows: Mild OHSS included abdominal distension, discomfort, mild nausea/vomiting and diarrhea. Moderate OHSS was considered as mild features + ultrasonographic evidence of ascites (Perpendicular fluid pocket of >9cm^2). Diagnosis of severe OHSS required clinical evidence of ascites and/or hydrothorax and breathing difficulties or one of the following criteria: 1) increased blood viscosity i.e. hematocrit at least 45%, or leucocyte count at least 20,000 per cubic millimeter. 2) coagulation abnormality 3) diminished renal perfusion and function (S. creatinine>1.2mg/dl) or 4) liver dysfunction, defined when transaminases (AST or ALT) are more than 40 u/ml. Critical OHSS was diagnosed in the presence of tense ascites or large hydrothorax, hematocrit >55%, or leucocyte count>25000 per cubic millimeter, anuria, thromboembolism or acute respiratory distress syndrome.

The secondary outcome included hospitalization rate, requirement of paracentesis, pregnancy rates and any side effects related of the medication used. The obtained data were compared with that obtained retrospectively.

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon (Z-test) ranked test for unrelated data and Chi-square (X^2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. *P* value <0.05 was considered statistically significant.

3. Results

The prospective part of the study comprised 60 PCOS patients with mean age of 27.3±2.9; range: 21-35 years and mean duration of infertility of 5.6±1.4; range: 3-9 years. There was non-significant difference between both of the prospective groups and the retrospective group as regards age, duration of infertility, anthropometric data or baseline hormonal levels. Details of enrollment data are shown in table 1.

All embryologic data showed non-significant difference between the studied groups, irrespective of the part of the study. Moreover, the reported clinical pregnancy rate was non-significantly higher in prospective versus retrospective parts with non-significantly higher clinical pregnancy rate with calcium infusion compared to bromocriptine therapy.

All patients completed the procedure and their designed course of therapy safely without complications or therapy-related side effects. Out of the 60 patients included in the prospective study 10 patients (16.7%) developed OHSS; 7 had mild and 3 patients had moderate manifestations with non-significant difference between both study groups as regards the frequency of OHSS (X^2=1.499, p>0.05) and that of moderate OHSS (X^2=0.248, p>0.05). On contrary; 13 out of the 30 patients (43.3%) included in the retrospective part of the study developed OHSS with significantly higher frequency (X^2=8.739, p<0.01) compared to those included in the prospective part, irrespective to preventive therapy. However, the difference in the frequency was more significant between groups A and C (X^2=5.202, p<0.01) than between groups A and B (X^2=3.113, p<0.05). Among those had OHSS in the retrospective part; 7 had mild and 5 had moderate manifestation and one patient developed severe manifestations necessitated hospitalization; an event that dose not occur in the prospective part. Concerning severity, there was significantly higher (X^2=3.468, p<0.05) frequency of high severity grades among patients of the retrospective versus the prospective part of the study, (Fig. 1).

Table (1): Patients enrollment data

		Retrospective part	Prospective part	
		Group A	Group B	Group C
Age (years)		26.8±2.9 (21-33)	27.7±3.1 (23-35)	27.3±2.8 (24-34)
Duration of infertility (years)		5.2±1.3 (3-7)	5.9±1.4 (4-9)	5.7±1.5 (3-8)
Anthropometric data	Weight (kg)	91±8.6 (78-109)	90.5±7.8 (80-104)	87.5±5.9 (76-103)
	Height (cm)	165.9±3.3 (162-172)	165.5±3.9 (160-173)	165.1±3.6 (159-170)
	BMI (kg/m^2)	33±2.8 (29-37.8)	33.1±2.8 (28.7-39.1)	32.1±2.2 (28.7-36.9)
Baseline hormonal assay	Serum E2	29.91±5.3 (23.9-45)	31.2±4.4 (26.5-44.1)	31.87±5.6 (26.6-49)
	Serum FSH	7.38±0.8 (5.78-9.08)	7.34±0.82 (6.1-9.28)	6.97±0.72 (6.12-8.67)

Data are presented as mean±SD; ranges are in parenthesis

Table (2): Embryological characteristics and cycle outcome in studied groups

Data		Group A	Group B	Group C
Number of oocytes retrieved		10.2±2.7	10.1±2.5	10.4±3
Number of metaphase II oocytes retrieved		9.2±2.3	9.1±2.2	9.3±2.7
Fertilization rate (%)		88.4±6.5	89.7±4.1	89±4.9
Number of available embryos	G1	3.4±1.1	4.4±1.4	4.2±1.3
	G2	3.1±1.6	3.8±1.3	4.1±1.8
	G3	0.3±0.5	0.27±0.4	0.23±0.4
Number of embryos transferred	G1	1.6±0.8	1.8±0.7	2±0.8
	G2	1.4±0.7	1.7±0.8	1.8±0.8
Implantation rate (%)		9.8±21.3	10.1±16.9	11.3±17.3
Clinical pregnancy rate (%)		8 (26.7%)	9 (30%)	11 (36.7%)
Frequency of OHSS among its severity grade	Mild	7 (23.3%)	4 (13.3%)	3 (10%)
	Moderate	5 (16.7%)	2 (6.6%)	1 (3.3%)
	Severe	1 (3.3%)	0	0

Data are presented as mean±SD & numbers; percentages are in parenthesis

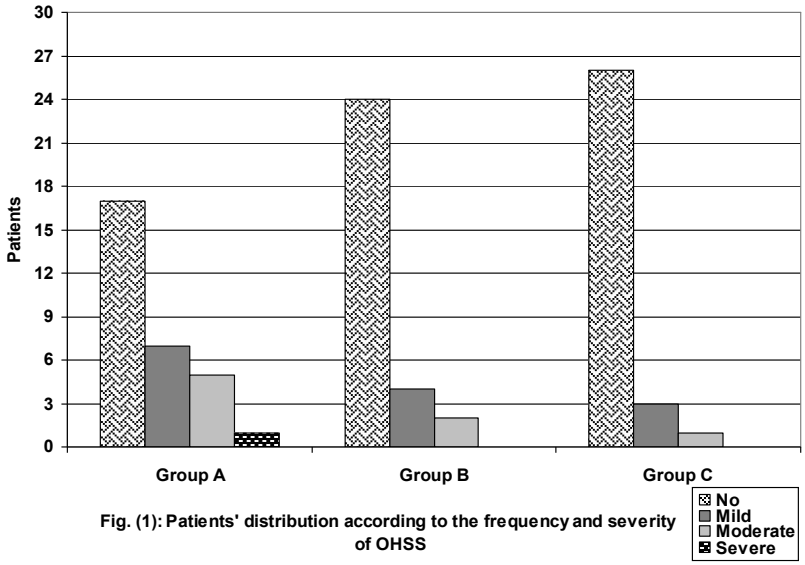

Fig. (1): Patients' distribution according to the frequency and severity of OHSS

4. Discussion

From the ethical point of view; the current study included a retrospective part so as to include 30 files for PCOS patients admitted for IVF or ICSI and fulfilling the inclusion criteria for the current study with files including all data required for the study, so the study included control group without exposing new patients to develop OHSS without preventive measures. Such policy for control group preparation was previously applied by **Spitzer *et al.* (2011)** who retrospectively investigated the frequency and severity of OHSS and the pregnancy rate in a patient collective at risk who received bromocriptine treatment and by **Gao *et al.* (2011)**, who retrospectively assessed the predictive value of endocrine gland-derived vascular endothelial growth factor concentrations in follicular fluid and serum for OHSS in patients undergoing controlled ovarian hyperstimulation.

For equalization of the results, there was non-significant difference between patients included in the prospective part of the study compared to data obtained retrospectively and patients included in the prospective part were randomly allocated in both groups. Prior to randomization, all patients included in the prospective part underwent cardiac evaluation to guard against cardiac problems associated with calcium infusion. Moreover, patients with history of gastritis and/or its complications were excluded from the study depending on the previously documented data of association of OHSS with nausea and/or vomiting and on the knowledge, according to package enclosed pamphlet, that bromocriptine therapy may induce gastrointestinal side effects.

The choice of PCOS patients for evaluation of preventive measures for OHSS in patients undergoing assisted reproductive technology relied on previous work of **Delvigne (2009)** who reported that after analyzing the data concerning the incidence of OHSS in relation to constitutional, clinical and ovarian response to stimulation data were analyzed as risk factors for development of OHSS and found that PCOS may be considered to be a risk factor for OHSS with an evidence level II, while for other risk factors, only evidence level III could be reached and concluded that PCOS patients are to be considered as potentially at risk for OHSS. Multiple explanations were provided for such high risk of OHSS; PCOS women are known to produce three times more follicles and oocytes than women with normal ovulatory function when stimulated according to similar protocol, **(Shulman and Dor, 1997)**, have an increased expression of vascular endothelial growth factor mRNA within the hyperthecal strom **(Kamat *et al.*, 1995)**, high ovarian volume **(Danninger *et al.*, 1996)**, lower resistance to blood flow in the stimulated ovaries **(Moohan *et al.*, 1997)**, and a high LH/FSH ratio >2, which suggests that LH dominance leads to disturbed androgen-estrogen conversion and high propensity for OHSS **(Bodies *et al.*, 1997)**. These previous studies documented and explained the liability of PCOS women as high-risk group for the development of OHSS.

All patients completed the procedure and their designed course of therapy safely without complications or therapy-related side effects. Out of the 60 patients included in the prospective study 10 patients (16.7%) developed OHSS; 7 had mild and 3 patients had moderate manifestations with non-significant difference between both study groups as regards the frequency of OHSS and that of moderate OHSS. On contrary; 13 out of the 30 patients (43.3%) included in the retrospective part of the study developed OHSS; 7 had mild and 5 had moderate manifestation and one patient developed severe manifestations necessitated hospitalization; an event that does not occur in the prospective part.

These data indicated the ability of the preventive therapy to significantly minimize the frequency and ameliorate the severity of OHSS in comparison to those did not receive preventive therapy.

These data go in hand with that previously reported in literature concerning the preventive therapy for OHSS; **Sherwal *et al.* (2011)**, assessed the effectiveness of dopamine agonist bromocriptine in reducing the incidence and severity of OHSS in patients undergoing assisted reproduction and reported a significant reduction in the incidence of moderate OHSS, early OHSS as well as the number of admissions with an incidence of clinically significant OHSS of 17.5% as compared to 40.9% in the control group with no difference was detected between the groups in clinical pregnancy rates. **Spitzer *et al.* (2011)**, retrospectively reported the ameliorating effect of bromocriptine on the frequency and severity of OHSS and **Wiwanitkit *et al.* (2011)** verified and documented these results. **Gurgan *et al.* (2011)**, evaluate the effectiveness of IV calcium infusion on prevention of OHSS in patients undergoing assisted reproductive techniques cycles and reported significant reduction of the frequency of OHSS with IV calcium infusion compared to control group and all the hyperstimulation cases in calcium group were mild, and there was no severe effect.

The obtained data and review of literature allowed concluding that prevention of OHSS in PCOS women committing ART is feasible and safe provided proper patient selection was followed. The non-significant difference between both modalities of OHSS prevention as regards clinical pregnancy rate and both the frequency and severity of OHSS opened the way for patients' preference of the preventive

modality and their general health status to be the selection guide.

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References

1. Beierwaltes WH: The role of calcium in the regulation of renin secretion. Am J Physiol Renal Physiol., 2010; 298:F1-11.
2. Bellver J, Munoz EA, Ballesteros A, Soares SR, Bosch E, Simón C: 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.
3. Bodies J, Torok A, Tinneberg HR: LH/FSH ratio as a predictor of ovarian hyperstimulation syndrome. Hum Reprod., 1997; 12:869-70.
4. Carizza C, Abdelmassih V, Abdelmassih S, Ravizzini P, Salgueiro L, Salgueiro PT: Cabergoline reduces the early onset of ovarian hyperstimulation syndrome: A prospective randomized study. Reprod Biomed Online. 2008; 17:751–5.
5. Costello MF, Chapman M, Conway U: A systematic review and meta-analysis of randomized controlled trials on metformin co-administration during gonadotrophin ovulation induction or IVF in women with polycystic ovary syndrome. Hum Reprod. 2006; 21:1387–99.
6. Danninger B, Brunner M, Obrucca A, Feichtinger W: Prediction of ovarian hyperstimulation syndrome by ultrasound volumetric assessment [corrected] of baseline ovarian volume prior to stimulation. Hum Reprod., 1996; 11:1597-9.
7. Delvigne A: Symposium: Update on prediction and management of OHSS. Epidemiology of OHSS. Reprod Biomed Online. 2009; 19(1):8-13.
8. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): A review. Hum Reprod Update. 2002;8:559–77.
9. 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(2):673-8.
10. Garcia-Velasco JA, Zuniga A, Pacheco A, Gómez R, Simón C, Remohí J: Coasting acts through down regulation of VEGF gene expression and protein secretion. Hum Reprod. 2004; 19:1530–8.
11. Gurgan T, Demirol A, Guven S, Benkhalifa M, Girgin B, Li TC: Intravenous calcium infusion as a novel preventive therapy of ovarian hyperstimulation syndrome for patients with polycystic ovarian syndrome. Fertil Steril. 2011; 96(1):53-7.
12. Huisman GJ, Fauser BC, Eijkemans MJ, Pieters MH: Implantation rates after *in vitro* fertilization and transfer of a maximum of two embryos that have undergone three to five days of culture. Fertil Steril., 2000; 73:117–122.
13. Kamat BR, Brown LF, Manseau EJ, Senger DR, Dvorak HF: Expression of vascular permeability factor/vascular endothelial growth factor by human granulosa and theca lutein cells. Role in corpus luteum development. Am J Pathol., 1995; 146:157-65.
14. Konig E, Bussen S, Sutterlin M, Steck T: Prophylactic intravenous hydroxyethyl starch solution prevents moderate-severe ovarian hyperstimulation in *in-vitro* fertilization patients: a prospective, randomized, double-blind and placebo-controlled study. Hum Reprod. 1998; 13:2421–4.
15. Kumar P, Sait SF, Sharma A, Kumar M: Ovarian hyperstimulation syndrome. J Hum Reprod Sci. 2011; 4(2):70-5.
16. Lamazou F, Legouez A, Letouzey V, Grynberg M, Deffieux X, Trichot C, Fernandez H, Frydman R: Ovarian hyperstimulation syndrome: pathophysiology, risk factors, prevention, diagnosis and treatment. J Gynecol Obstet Biol Reprod (Paris). 2011; 40(7):593-611.
17. Moohan JM, Curcio K, Leoni M, Healy D, Hurley V: Low intra ovarian vascular resistance: a marker for severe ovarian ovarian hyperstimulation syndrome. Fertil Steril., 1997; 67:728-32.
18. Ortiz-Capisano MC, Ortiz PA, Harding P, Garvin JL, Beierwaltes WH: Decreased intracellular calcium stimulates renin release via calcium inhibitable adenylyl cyclase. Hypertension 2007; 49:162-9.
19. Rajesh H, Lee WY, Fook-Chong S, Yu SL. Ovarian hyperstimulation syndrome: an analysis of patient characteristics in the Asian population. Singapore Med J. 2011; 52(3):168-74.
20. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group: Revised 2003 consensus on diagnostic criteria and long-term

health risks related to polycystic ovary syndrome. Fertil Steril., 2004; 81:19–25.
21. Sherwal V, Malik S, Bhatia V: Effect of bromocriptine on the severity of ovarian hyperstimulation syndrome and outcome in high responders undergoing assisted reproduction. J Hum Reprod Sci. 2010; 3(2):85-90.
22. Shulman A, Dor J: *In vitro* fertilization treatment in patients with polycystic ovaries. J Assist Reprod Genet 1997; 14:7-10.
23. Soares SR, Gomez R, Simon C, Garcia-velasco JA, Pellicer A: Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update 2008; 14:321-33.
24. Spitzer D, Wogatzky J, Murtinger M, Zech MH, Haidbauer R, Zech NH: Dopamine agonist bromocriptine for the prevention of ovarian hyperstimulation syndrome. Fertil Steril. 2011;95(8):2742-4.
25. Steer CV, Mills CL, Tan SL, Campbell S, Edwards RG. The cumulative embryo score: a predictive embryo scoring technique to select the optimal number of embryos to transfer in an *in-vitro* fertilization and embryo transfer programme. Hum Reprod. 1992; 117: 7-9.
26. Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M: Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. Fertil Steril. 2010;93:2281–4
27. Vlahos NF, Gregoriou O. Prevention and management of ovarian hyperstimulation syndrome. Ann NY Acad Sci. 2006;1092:247–64
28. Wiwanitkit V: Ovarian hyperstimulation syndrome. Singapore Med J. 2011; 52(5):381
29. Yakovenko SA, Sivozhelezov VS, Zorina IV, Dmitrieva NV, Apryshko VP, Voznesenskaya JV: Prevention of OHSS by intravenous calcium. Hum Reprod., 2009; 24(Suppl 1): i61.

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