

# Follicular Aspiration Is Superior to Coasting as Effective Prophylactic Procedure against Ovarian Hyperstimulation Syndrome

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## Abstract

**Objectives:** Evaluation of outcome follicular aspiration compared to coating procedure for infertile women undergoing ICSI regarding frequency and severity of ovarian hyperstimulation syndrome (OHSS). **Patients & Methods:** Infertile PCOS women underwent controlled ovarian stimulation with luteal phase GnRH-agonist long down-regulation protocol. Women developed serum E<sub>2</sub> level > 4000 pg/ml and/or >20 follicles of ≥10 mm in diameter were randomly divided to receive coasting strategy (Coasting group) or TVU-guided aspiration (Aspiration group). When ≥3 follicles were ≥18 mm and serum E<sub>2</sub> level was <3000 pg/ml, GnRH agonist was continued, and 10,000 IU was administered 36 h before oocyte retrieval, and ICSI was performed 72-hr thereafter and the frequency of moderate-to-severe OHSS was determined. **Results:** 82 women developed criteria for categorization and 21 women (25.6%) developed moderate-to-severe OHSS; 5 women of aspiration and 16 of Coasting group; with significantly (P = 0.005) lower frequency in aspiration group. Twenty women developed ascites; 3 women had clinically detectable, while 17 women had US detected ascites with significantly (P = 0.039) higher frequency among women that had coasting. All other manifestations of OHSS were significantly lower with aspiration procedure. Both coasting and aspiration therapy significantly reduced serum E<sub>2</sub> and ovarian diameter on day of hCG injection compared to estimates taken at time of categorization. **Conclusion:** Coasting procedure prior to hCG injection could decrease incidence of OHSS and lessens its manifestation. Follicular aspiration provided more superior results and improved outcome of these women. Any of these modalities could be provided to infertile high-risk women according to the availability of experiences and patients' selection.

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## Keywords

Ovarian Hyperstimulation Syndrome, PCOS, Follicular Aspiration, Coasting Procedure

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## 1. Introduction

Ovarian stimulation (OS) is crucial for pregnancy success in assisted reproductive technology treatments [1]. However, ovarian hyperstimulation syndrome (OHSS) in hyper-responders to OS is common despite being self-limited [2]. It is a severe complication for patients undergoing IVF/ICSI [3]. Vascular endothelial growth factor (VEGF) plays the most important role in pathogenesis of OHSS and is related to concomitant increased capillary permeability and fluid retention [2].

Presence of genetic mutations is already known to be involved in OHSS [4]. Women who had follicle-stimulating hormone receptor variant asparagine/serine in amino acid 680 are at higher risk for OHSS during IVF [5]. Also, a potential link was suggested between OHSS and mutations of the FLT4 gene which encodes Fms-related tyrosine kinase 4 [4]. Production of some pro-inflammatory molecules such as IL-8, IL-1, IL-6 and TNF- $\alpha$  was incriminated in pathogenesis of OHSS [2].

Therapeutic options to reduce the incidence and lessen the severity of OHSS are variant and with contradictory results [6]. The “freeze-all” strategy provides benefit for high-responder women who were at risk of OHSS, but should not be offered universally [7]. Addition of hp-hMG on day of antagonist initiation significantly lowers OHSS rates [8]. In sequential ovarian stimulation cycles, individualized doses of follitropin delta decreased the risk of moderate/severe OHSS than conventional follitropin alfa regimen [9].

Multiple drugs were evaluated for prophylaxis against or treatment of OHSS [10]. In rat model of OHSS, administration of myo-inositol and metformin significantly reduced VEGF expression and decreased vascular permeability [11]. Prophylactic vitamin D supplemental therapy effectively increased pigment epithelium-derived factor which protected against OHSS [12]. Montelukast [13] and resveratrol [14] induced reduction of ovarian diameter and VEGF expression.

Coasting is a well-known strategy to decrease severity of OHSS [15] and acceleration of coasting in cases of OHSS through treatment with GnRH-ant after pituitary suppression with GnRH reduces estradiol (E2) level, and avoids cycle cancellation with prevention of OHSS [16]. Thus, the current study tried evaluation of outcome follicular aspiration compared to coating procedure for infertile women undergoing ICSI regarding the frequency and severity of OHSS.

## 2. Design

Prospective comparative clinical trial.

### 3. Setting

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### 4. Patients & Methods

The study protocol was approved by the Local Ethical Committee. All PCOS infertile women assigned to undergo ICSI cycles since June 2016 were eligible for evaluation. Inclusion criteria included the presence of at least 20 pre-ovulatory follicles in both ovaries with serum E<sub>2</sub> level  $\geq 3000$  pg/ml in PCOS women. PCOS was diagnosed according to Rotterdam criteria depending on the presence of at least two of oligomenorrhic and/or anovulatory cycles, clinical and/or biochemical signs of hyperandrogenemia with serum total testosterone level  $> 0.8$  ng/ml and polycystic ovaries containing  $> 12$  follicles of 2 - 9 mm in diameter and/or an ovarian volume  $> 10$  ml per ovary by vaginal ultrasound [17]. Exclusion criteria included BMI  $> 30$  kg/m<sup>2</sup>, history of previous development of OHSS, endocrinopathies, maintenance on insulin-sensitizing drugs, receiving GnRH antagonists.

All women underwent controlled ovarian stimulation (COS) with luteal phase GnRH-agonist long down-regulation protocol using subcutaneous injection of Triptorelin acetate 0.1 daily (DecapeptylGyn™; Ferring, Kiel, Germany) on 21<sup>st</sup> day of cycle that precede stimulation. Adequate pituitary desensitization was established on 2<sup>nd</sup> or 3<sup>rd</sup> day of menses and ovarian stimulation with gonadotropins was started on 3<sup>rd</sup> day of the oncoming cycle by the use of recombinant-FSH (r-hFSH, Gonal-F®, 75 UI, Serono, Switzerland) at a daily dose 75 - 150 IU according to the individual response to treatment for 5 - 7 days. Follow-up consisted of estimation of serum E<sub>2</sub> every 2 days and ultrasonographicscanning by 7 - 10 MHz probe (Voluson 730 PRO V, GE Healthcare, USA) was done every 3 - 5 days.

Women developed serum E<sub>2</sub> level of  $>4000$  pg/ml and/or sonographic detection of  $>20$  follicles each of  $\geq 10$  mm in diameter and at least 20% of follicles were  $\geq 15$  mm diameter were included in the trial and were randomly, using sealed envelopes, divided into two equal groups: Coasting group included women underwent coasting strategy and Aspiration group included women underwent follicular aspiration. For coasting group, serum E<sub>2</sub> and FSH levels were measured from the day of coasting until the day of hCG administration. For women of aspiration group, TVU-guided oocyte retrieval was performed under propofol sedation using single-lumen 17-gauge needle (Cook Ireland, Limerick, Ireland) at maintained pressure of 80 mmHg.

When at least three follicles reached a mean diameter of  $\geq 18$  mm and serum E<sub>2</sub> level was  $<3000$  pg/ml, GnRH agonist was continued and a single intramuscular injection of 10,000 IU hCG (Choriomon, IBSA, Switzerland) was administered 36 h before the planned time of oocyte retrieval and then ICSI was performed, 72-hr thereafter, a maximum of two embryos were transferred, as described previously by Huisman *et al.* [18]. All embryos were scored according to

Steer *et al.* [19] on day of transfer and embryos in G1 and G2 grade having 4 blastomeres on day 2 or  $\geq 8$  blastomeres on day 3, less than 20% fragmentation, and no multinuclear blastomeres were transferred. Luteal phase support was started the day after ovum pick up by the vaginal administration of progesterone (Cyclogest 200 mg suppositories; Actavis UK Limited) twice daily for 16 days and was continued for up to 12 weeks if pregnancy occurred.

## 5. Diagnosis and Classification of OHSS

OHSS was diagnosed according to the criteria of Golan *et al.* [20] as mild OHSS on presence of abdominal distension and discomfort (Grade 1) with nausea, vomiting and/or diarrhea and ovarian enlargement up to 12 cm (Grade 2). Moderate OHSS (Grade 3) was diagnosed in patients had clinical presentation of grade 2 OHSS plus ultrasonographic evidence of ascites. OHSS was considered severe (Grade 4) if there was clinical evidence of grade 3 OHSS plus clinical evidence of ascites and/or hydrothorax, breathing difficulties; and was considered as severe OHSS of grade 5 if patient of grade 4 developed increased blood viscosity due to hemoconcentration, as well as decreased renal perfusion [21].

## 6. Evaluated Parameters

- 1) Primary outcome is the frequency of moderate-to-severe OHSS.
- 2) The secondary outcome included the following items:
  - Presence and severity of abdominal pain was graduated using a numerical pain visual analogue scale (VAS) with 0 means no pain and 10 means severe intolerable pain [22].
  - Nausea and/or vomiting and sense of abdominal distension were scored using verbal analogue scale as nil, mild, moderate, and severe symptom.
  - Hospitalization rate and requirement of paracentesis.

## 7. Statistical Analysis

Obtained data were presented as mean  $\pm$  SD, numbers and percentages. Results were analyzed using One-way ANOVA test, Student t-test and Chi-square test ( $X^2$  test). Statistical analysis was conducted using the IBM SPSS (Version 23, 2015) for Windows statistical package. P value  $< 0.05$  was considered statistically significant.

## 8. Results

Throughout the duration of the study, 82 women developed criteria for categorization (Figure 1). There were non-significant differences between women of both groups as regards basal data of enrolled women (Table 1).

At time of categorization, serum E2 levels increased significantly in all patients compared to their respective basal E2 levels. On day of hCG injection, estimated serum E2 levels significantly decreased in patients of both groups in comparison to levels estimated at time of categorization, but were still significantly higher compared to basal E2 levels. Serum E2 levels estimated at time of

categorization were non-significantly lower in patients who underwent aspiration than patients undertook coasting procedure. On the other hand, serum E2 levels estimated on day of hCG injection were significantly lower in patients of aspiration group than in patients of coasting group (**Figure 2**). On day of hCG injection, serum FSH levels were significantly increased in all studied patients in comparison to corresponding levels estimated at time of categorization with non-significantly higher levels were estimated in women of aspiration group than women of coasting group (**Table 2**).

On day of hCG injection, ovarian diameter estimated in all studied patients was significantly decreased compared to their respective diameter determined at time of categorization with significantly smaller ovarian diameter in patients of aspiration group than in patients of coasting group (**Table 2, Figure 3**).

Considering the primary outcome; 21 women developed moderate-to-severe OHSS for a frequency of 25.6% (**Figure 1**). Seventeen women developed moderate OHSS and only four women developed severe OHSS of grade 4 and no women developed severe OHSS of grade 5. Only five women of aspiration group, while 16 women of Coasting group developed moderate-to-severe OHSS with significantly ( $P = 0.005$ ) lower frequency in aspiration group. The remaining 61 women developed mild OHSS; 36 and 25 in aspiration and coasting groups, respectively (**Figure 4**).

Twenty women developed ascites; 14 in coasting and 6 in aspiration groups. Three women; 2 in coasting and one in aspiration groups, had clinically detectable ascites, while 17 women had US detected ascites clinically received coasting treatment with significantly ( $P = 0.039$ ) lower frequency of ascites among women of aspiration group. All women developed abdominal distension of varied grades, but women received aspiration showed significantly ( $P = 0.002$ ) lower distension score than women of coasting group. Nausea and vomiting occurred in 73 women and 47 women, respectively with significantly lower scores in women of aspiration versus coasting group. All women had pain with varied scores with significantly lower scores among women of aspiration group (**Table 3**). Twelve patients (14.6%) required hospitalization; 8 patients in Coasting and 4 patients in aspiration group with non-significantly ( $P = 0.211$ ) lower frequency of hospitalization in aspiration group, but no patient required paracentesis.

**Table 1.** Data of studied women at time of evaluation.

Group Data	Coasting (n = 41)	Aspiration (n = 41)	P value
Age (years)	27.5 ± 4.3	28.3 ± 3.8	0.522
Weight (kg)	82 ± 4.4	80.8 ± 5.6	0.109
Height (cm)	167.1 ± 3.4	166.3 ± 4	0.609
BMI (kg/m <sup>2</sup> )	29.4 ± 1.3	29.2 ± 1.9	0.327
Duration of infertility (years)	5.7 ± 1.5	6.2 ± 2	0.287
Basal FSH level (IU/L)	7.7 ± 1.4	7.5 ± 1	0.323
Basal E <sub>2</sub> level (pg/ml)	3162.4 ± 579	3295.5 ± 479	0.219

Data are presented as mean ± SD;  $P > 0.05$  indicates insignificant difference between both groups.

**Table 2.** Data of studied women determined on day of hCG injection.

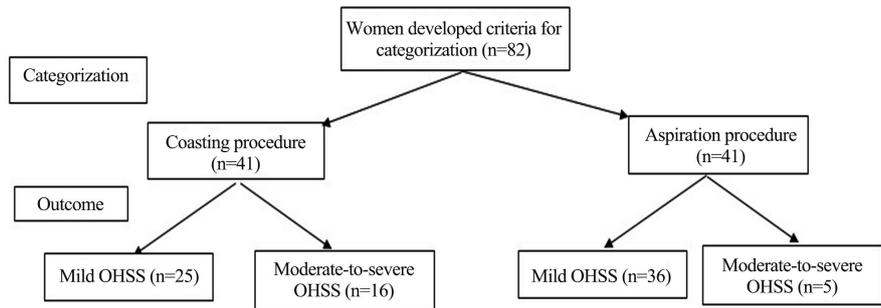
Group Variable Time	Coasting (n = 41)	Aspiration (n = 41)	P value	
Basallevel	3162.4 ± 579	3295.5 ± 479	0.219	
Categorization	7150.5 ± 1016	6602 ± 1495.4	0.056	
E <sub>2</sub> level (pg/ml)	Day of hCG injection	6579.3 ± 1240	5827.2 ± 1498.6	0.015
	P1	<0.001	<0.001	
	P2	0.025	0.022	
	Categorization	7.7 ± 1.4	7.8 ± 1.6	0.719
FSH level (IU/L)	Day of hCG injection	9 ± 3.4	9.7 ± 3.8	0.386
	P2	0.027	0.01	
	Categorization	14.9 ± 5.8	14.3 ± 5.4	0.461
Ovarian diameter (cm)	Day of hCG injection	12.4 ± 3.9	10.5 ± 4.7	0.047
	P2	0.028	0.001	

Data are presented as mean ± SD; P indicates insignificance of difference between both groups; P1: indicates significance of difference in E<sub>2</sub> serum levels between basal and at categorization levels; P2: indicates significance of difference between measures estimated at time of categorization and on day of hCG injection; P < 0.05: indicates significant difference; P > 0.05: indicates non-significant difference.

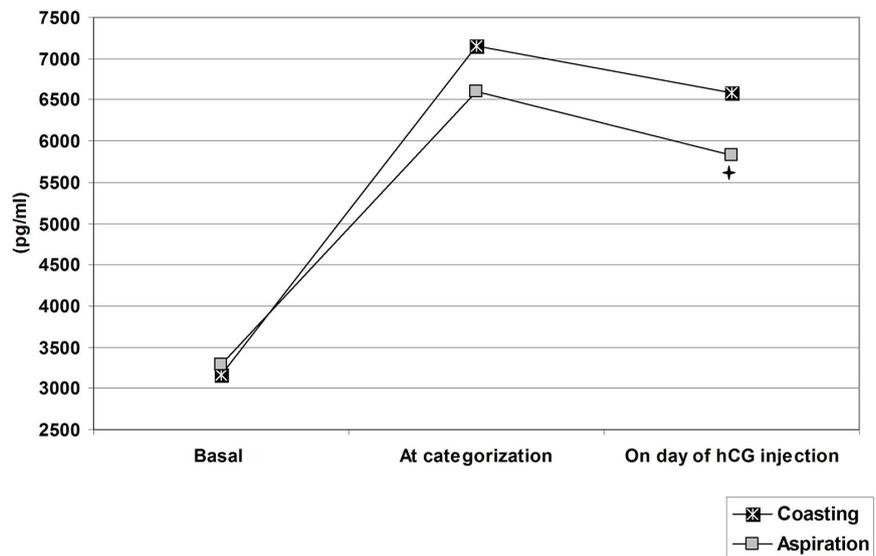
**Table 3.** OHSS manifestations scoring of women enrolled in both groups.

Manifestations		Score					
Score items		1	2	3	4	Total	
Abdominal distension	Group	Coasting	7 (17%)	16 (39%)	17 (41.5)	1 (2.5%)	2.3 ± 0.8
		Aspiration	19 (46.3%)	14 (34.2%)	8 (19.5%)	0	1.7 ± 0.7
	P value			0.031		0.002	
Nausea	Group	Coasting	7 (17%)	23 (56.1%)	9 (22.5%)	2 (4.9%)	1.7 ± 0.8
		Aspiration	2 (4.9%)	14 (34.2%)	19 (46.3%)	6 (14.6%)	1.1 ± 0.7
	P value			0.015		0.0015	
Vomiting	Group	Coasting	14 (34.2%)	16 (39%)	11 (26.8%)	0	1 ± 0.8
		Aspiration	21 (51.2%)	17 (41.5)	3 (7.3%)	0	0.6 ± 0.6
	P value			0.049		0.009	
Pain	Group	Coasting	2	3	4	5	Total
		Coasting	10 (24.4%)	17 (41.5)	11 (26.8%)	3 (7.3%)	3.2 ± 0.9
	Aspiration	19 (46.3%)	16 (39%)	5 (12.2%)	1 (2.5%)	2.7 ± 0.8	
P value			0.108		0.007		

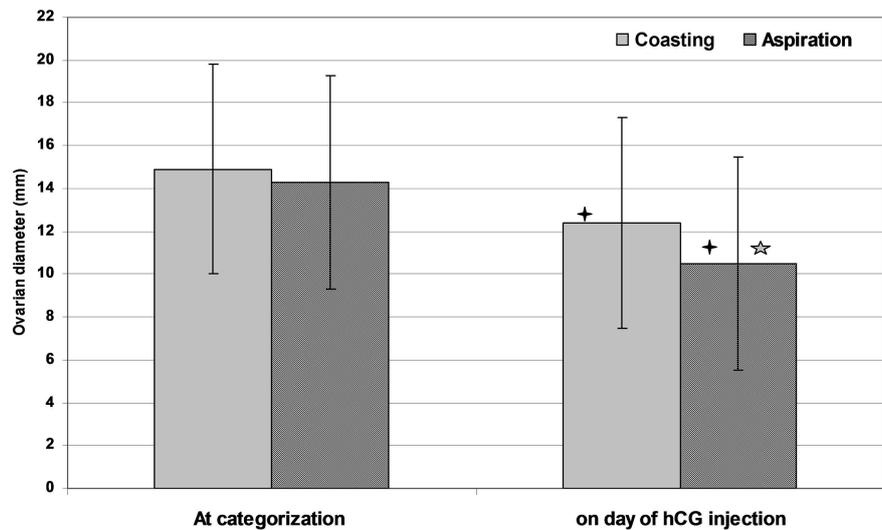
Data are presented as numbers & percentages; P indicates insignificance of difference between both groups.



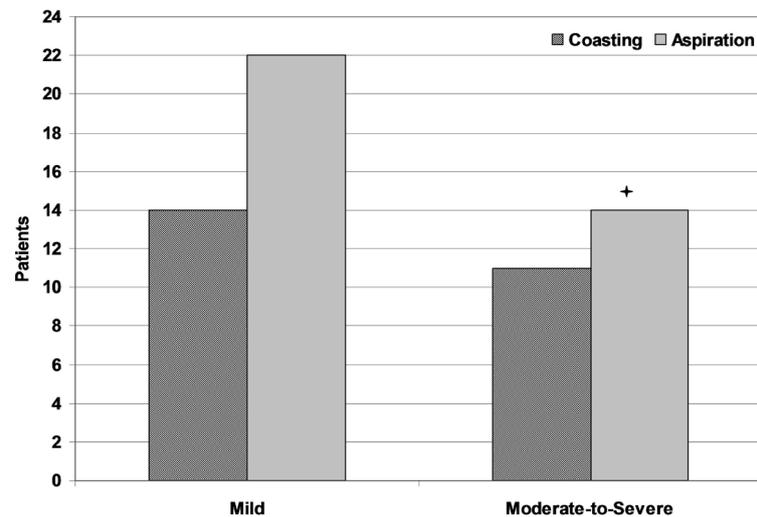
**Figure 1.** Consort Flow sheet.



**Figure 2.** Mean serum E2 levels estimated in patients of both groups (+ indicates significant inter-group difference).



**Figure 3.** Mean ( $\pm$ SD) ovarian diameter estimated at time of cate gorization and on day of hcG injection in women of both groups (+ significant difference versus at categorization; ☆ significant inter-group difference).



**Figure 4.** Patients' distribution according to severity of OHSS (+ indicates significant inter-group difference).

## 9. Discussion

The therapeutic policies provided for patients of both groups did favorably as manifested by the significant reduction of serum E2 and ovarian diameter on day of hCG injection in comparison to estimates taken at time of categorization. These results point to a fact that in women at high-risk for development of OHSS, certain therapeutic modalities could ameliorate or lessen its manifestations down to acceptable level. In support of this assumption, no patient developed severe OHSS of grade 5, only three women developed clinically detectable ascites, but no patient required paracentesis. Furthermore, about 75% of patients developed mild symptoms ranging between grade one and two.

The obtained results concerning patients received coasting procedure are in line D'Angelo *et al.* [23] who reviewed RCT assessed the effect of coasting on prevention of OHSS and reported lower rates of OHSS with coasting versus no coasting by rates suggesting that if 45% of women developed moderate or severe OHSS without coasting, only 4% - 17% would develop it with coasting. Also, Abide Yayla *et al.* [24] in their retrospective study of women used coasting to avoid OHSS in 100 high-risk women and documented that all women had reached to embryo transfer stage and reported clinical pregnancy rate of 44%. Also, Kailasam *et al.* [25] prospectively, found coasting for 6 days with subsequent blastocyst transfer may be an effective strategy for patients at risk of OHSS with no detrimental effects on blastocyst development or live birth outcome

Concerning comparative study for coasting and follicular aspiration as preventive strategy for OHSS, D'Angelo *et al.* [25] reviewed literature for RCT assessing the efficacy of coasting versus unilateral follicular aspiration and documented that data were not pooled due to heterogeneity. Moreover, review of recently published articles detected only one study compared the effect of coasting versus aspiration on incidence of OHSS; however, that study reported no difference between follicular reduction prior to HCG and coasting, in terms of OHSS

reduction as a primary endpoint [26], these results are contradictory to the result of the current study and this difference could be attributed to multiple imitations of Bushaquer's study [26], firstly, the sample size is small; 39 women were divided into two study groups and 8 women developed OHSS; 6 versus 2 women in each group, respectively but these numbers could not reach the appropriate limit for statistical analysis to be significant or non-significant. Secondly, Bushaquer's study [26] did not comment on the frequencies of OHSS severity manifestations, which are more important than the sole frequency of OHSS.

On the other hand, the current study reported significantly reduced OHSS manifestations, both as frequency and severity, with follicular aspiration than with coasting, so the current study approved the efficacy and safety of follicular aspiration in comparison to coasting despite of proved efficacy of coasting. In support of these findings, an early study conducted by Zhu *et al.* [27] had documented that follicular aspiration during the selection phase can prevent severe OHSS and reduce OHSS prevalence in patients with PCOS undergoing COH. More recently, Haydardedeoglu *et al.* [28] documented that in poor responders both follicular aspiration and flushing has similar results, but follicular flushing is time consuming.

The reported clinical effectiveness of coasting could be attributed to affecting follicles, especially immature follicles, through apoptosis with significant decrease in VEGF expression and secretion [29] [30]. Thus, coasting acts through inhibition of VEGF protein transcription and translation which is a time-consuming process and is unpredictable to be absolute inhibition. On the other hand, follicular aspiration allows removal of the already formed VEGF thus rapidly eliminating its effect and giving no chance by oocyte removal for re-synthesis of growth factors [31] [32]. Additionally, aspiration removes other cytokines that may have a role in induction of OHSS as IL-2 which increased levels induce vascular dilatation syndrome [33]. IL-17 [34] melatonin and melatonin receptor 2 [3] that were reported to be correlated with incidence and severity of OHSS. These data could explain the reported superior clinical effect of aspiration in comparison to coasting procedure.

## 10. Conclusion

Coasting procedure prior to hCG injection could decrease the incidence of OHSS and lessens its manifestation. However, follicular aspiration provided more superior results and improved outcome of these women. Any of these modalities could be provided to infertile high-risk women according to the availability of experiences and patients' selection. Wider scale studies are mandatory to establish the results and to evaluate underlying mechanisms for the reported clinical effectiveness of these procedures.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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