Incidence of ovarian hyperstimulation Syndrome among patients with polycystic ovarian syndrome undergoing IVF/ICSI

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Abstract

Background: IVF/ICSI is the preferred treatment option for PCOS-related infertility, however, the risk of ovarian hyperstimulation syndrome (OHSS) is significantly increased.

Aim: Therefore, this study was conducted to estimate incidence and degree of OHSS among PCOS women underwent IVF/ICSI after taking different stimulation protocol in Mansoura fertility unit.

Methods: The study enrolled 108 PCOS cases underwent IVF/ICSI. OHSS occurrence was detected and possible risk factors for moderate to severe OHSS were studied.

Results: Results revealed that the group of (Antagonist protocol with a GnRH Agonist trigger) had 2.2% OHSS incidence. The group of (Antagonist protocol plus hCG trigger) had an OHSS incidence of 22.6%. The group of (Long Agonist protocol plus hCG trigger) had an OHSS incidence of 25%. The choice of IVF/ICSI protocol (e.g. pituitary suppression protocol, oocyte maturation trigger & freeze all vs fresh embryo transfer) in addition to multiple demographic (e.g. Age & BMI), historical (e.g. LOD), clinical (e.g. AFC), laboratory (e.g. AMH) and follow up (e.g. E2 level at trigger day, Number of follicles >18mm, Number of oocytes retrieved, Number of transferred embryos, Clinical pregnancy, multiple pregnancy) factors affected OHSS incidence significantly.

Conclusion: To reduce the likelihood of Ovarian Hyperstimulation Syndrome (OHSS) occurring, certain measures can be taken, including employing the GnRH antagonist protocol for inhibiting the pituitary gland and Stimulating ovulation through the use of a GnRH agonist, as well as cryopreservation of all embryos (IVF/ICSI cycle segmentation). Close monitoring of PCOS patients during IVF/ICSI with treatment plans individualization.

Keywords: Polycystic Ovary Syndrome (PCOS), In Vitro Fertilization/Intracytoplasmic Sperm Injection (IVF/ICSI), Ovarian Hyperstimulation Syndrome (OHSS), Human Chorionic Gonadotropin (hCG), Laparoscopic Ovarian Drilling (LOD), Estradiol (E2), Gonadotropin-Releasing Hormone (GnRH), Anti-Mullerian Hormone (AMH), Antral Follicle Count (AFC), Body Mass Index (BMI)..

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is an ovarian stimulation complication used for yielding numerous ovarian follicles simultaneously which is an important step during assisted reproductive techniques. OHSS is a rare side effect that has different degrees of severity including mild, moderate up to severe & even lethal (1). The most important dangers are linked to moderate & severe OHSS resulting in thromboembolic accidents, acute renal impairment & respiratory distress requiring assisted ventilation (2, 3).

The rate of incidence of OHSS in PCOS patients undergoing IVF/ICSI significantly increased up to 13.9 times more than the incidence in non PCOS patients diagnosis (4). The definite etiology of OHSS is not known. The management is empirical and so prophylaxis is the top management line of OHSS (5).

Recognizing risk factors and predictive factors for OHSS and individualizing the controlled ovarian stimulation (COS) protocol in a good manner is the most important step in the primary prophylaxis of OHSS, because each individual has his own response to each COS strategy as regard to risks and benefits (6).

Patients and Methodology

This retrospective research was carried out in Mansoura Fertility Unit and Mansoura university hospitals during the period from January 2016 to March 2020. The study included 108 infertile PCOS patients diagnosed by criteria of (7) who were aged 18 to 40 years of age and have undergone IVF/ICSI procedures. But we excluded Patients who were infertile due to factors other than PCOS e.g. severe male factor (azoospermia), severe endocrinal disorders (severe thyroid dysfunction and/or severe hyperprolactinemia) and anatomical causes of infertility e.g. Uterine hypoplasia, bicornuate uterus and unicornuate uterus.

Consideration of ethics

Research protocol was submitted and received approval from the Medical Research Ethical Committee at Faculty of Medicine, Mansoura University (code: MS.20.02.1027). It was submitted and officially approved by the board of obstetrics and gynecology departments, Mansoura University.

Methods

Data from the cycles of IVF/ICSI of PCOS patients were collected from the fertility unit records. Data on OHSS outcomes were obtained from the medical records of the patients in the obstetrics and gynecology departments of Mansoura University hospitals. Collected patients' data included:

- Base line demographic data e.g. age, BMI, Infertility type, Infertility duration, Basic investigations e.g. semen analysis, HSG, hormonal assay (e.g. FSH, LH, TSH, Prolactin, AMH) and AFC by US in day 2 of cycle.
- Past medical and surgical history whether +ve or -ve.
- Data related to OHSS e.g. past hx of OHSS, grade, type, E2 level at trigger day, Lab. Investigations (e.g. WBCs count, Hematocrit, serum albumin level, SGOT, SGPT, serum creatinine level, platelet count), ascites whether +ve or -ve, US findings (e.g. dominant follicle size and number of follicles >18mm), hospital admission.
- Data related to oocytes and embryo grading e.g. count of oocytes collected, count of embryos, freeze all or not, fresh embryo transfer or not, number of transferred embryos of grade A(D3).
- Pregnancy data e.g. chemical pregnancy, clinical pregnancy, ongoing clinical pregnancy (viable), multiple pregnancy.

- Data of symptoms, signs and management modalities of OHSS according to its grade e.g. thromboembolic events, ascites, pleural effusion, coagulation abnormalities, multiple system failure, renal shut down, paracentesis, LMWH administration, intensive critical care and albumin administration.

This data was processed statistically to determine OHSS incidence, degree and risk factors.

Outcomes

Primary outcomes

- Incidence of OHSS: "proportion of patients who develop Ovarian Hyperstimulation Syndrome within a specific group." It is typically expressed as a percentage. This statistic helps assess the risk of OHSS associated with different treatment approaches.

Secondary outcomes

- OHSS grade is a classification system used to categorize the severity of Ovarian Hyperstimulation Syndrome (OHSS). This system typically categorizes OHSS into different grades based on specific criteria, such as symptoms, physical exam findings, and ultrasound scans. Each grade reflects the increasing intensity of OHSS presentation. It's used to assess the risk associated with Various protocols for ovarian stimulation.
- **BMI and OHSS:** The correlation between the body mass index of the patient (BMI) and the likelihood of them developing OHSS.
- **Age and OHSS:** These describe how a patient's age can be a factor in developing OHSS.
- **Clinical pregnancy and OHSS:** correlation between pregnancy and OHSS incidence.
- **AFC by US on day 2 of cycle and OHSS incidence:** This explains how a particular ultrasound metric, the count of antral follicles (AFC), can be employed to evaluate the risk of OHSS. AFC quantifies the count of tiny follicles in the ovaries on the second day of a menstrual cycle.
- **AMH and OHSS incidence:** The correlation between AMH and OHSS refers to the **statistical association** between the level of anti-Müllerian hormone (AMH) in a woman and her **possibility of experiencing ovarian hyperstimulation syndrome (OHSS) during** fertility treatment.
- **Laparoscopic ovarian drilling and OHSS: The relationship between laparoscopic of ovarian drilling (LOD) and OHSS** refers to the potential impact of a surgical procedure called **laparoscopic ovarian drilling** on the possibility of experiencing ovarian hyperstimulation syndrome (OHSS) during fertility treatment.

Estradiol level at trigger day and OHSS: The relationship between estradiol level at trigger day and OHSS refers to the potential **association** between the concentration of the hormone **estradiol** assessed on the day of ovulation trigger **(trigger day)** and the potential for developing **ovarian hyperstimulation syndrome (OHSS)** during fertility treatment.

Analysis of Statistical Data

We entered and processed data using IBM-SPSS software Version 26.0. Qualitative data was represented as N (%), and quantitative data was denoted as mean, standard deviation (SD). Quantitative data was initially examined for normality using Shapiro-Wilk's test and Kolmogorov-Smirnov's test, with data deemed normally distributed if $p>0.05$. The existence of significant outliers (extreme values) was verified by inspecting boxplots. For qualitative data across groups, the Chi-Square (χ^2) test was employed if the expected count in all cells was ≥ 5 (adequate

sample size), otherwise Fisher's exact test was utilized. The Independent-Samples t-test was applied to compare quantitative data that follows a normal distribution between two groups. One way ANOVA (One way Analysis Of Variance) was used to compare normally distributed quantitative data among more than two groups using the F-test. The Mann-Whitney U test was employed for non-parametric data. A P value less than or equal to 0.05 was considered to be significant.

Results

The group following the Antagonist protocol in addition to a GnRH Agonist trigger had an OHSS incidence of 2.2%. The group following the Antagonist protocol along with an hCG trigger had an OHSS incidence of 22.6%. The group following the Long Agonist protocol along with an hCG trigger had an OHSS incidence of 25%. Due to limitations in the chi-square test for contingency tables with small sample sizes ($n < 5$), particularly evident in the observed incidence of OHSS in the first group, Fisher's exact test was used for P-value calculation. To ensure precise estimation of P-values with this test, a modified 2x2 contingency analysis was conducted. There was a significant difference in OHSS incidence between the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Antagonist protocol with an hCG trigger (p1), as well as between the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Long Agonist protocol with an hCG trigger (p3). However, no significant difference detected between the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger (p2). (Table 1).

Table (1) Incidence of Ovarian Hyperstimulation Syndrome (OHSS) among groups of different IVF/ICSI protocols according to both pituitary suppression protocol & oocyte maturation trigger.

		(Ant.+Agonist trig.) group (45 patients)	(Ant.+HCG) group (31 patients)	(Long Ag.+HCG) group (32 patients)	P1	P2	P3
Incidence of OHSS N(%)	No	44 (97.8%)	24 (77.4%)	24 (75%)	0.005*	0.8	**0.002***
	Yes	1 (2.2%)	7 (22.6%)	8 (25%)			

*A P-value is considered significant if it is ≤ 0.05. The percentages displayed in the table are within-group percentages. The 1st Group followed the Antagonist protocol with a GnRH Agonist trigger, the 2nd Group followed the Antagonist protocol with hCG trigger, and the 3rd Group followed the Long Agonist protocol with hCG trigger. P1 represents the P-value for the difference between the 1st and 2nd groups, P2 represents the P-value for the difference between the 2nd and 3rd groups, and P3 represents the P-value for the difference between the 1st and 3rd groups.

A non-significant difference in baseline characteristics, including age, BMI, type/duration of infertility, antral follicle count (AFC), and hormonal assays, were observed among patients undergoing different IVF/ICSI protocols. To enable a statistical comparison of semen analysis and hysterosalpingography results among patients undergoing various IVF/ICSI protocols, a 2x2 contingency analysis was employed. This method was chosen considering the limited sample size, as it ensures a more precise calculation of the P-value (statistical

significance) using Fisher's exact test. According to the baseline demographic data, no statistically significant variation ($p > 0.05$) was observed between either semen analysis or hysterosalpingography results and the different patient groups in the present study. A review of the patients' medical history, including laparoscopic ovarian drilling showed no differences among the various patient groups. (Table 2)

Table (2): Base line of demographic data.

		(Ant.+Agonist trig.) group (45 patients)	(Ant.+HCG) group (31 patients)	(Long Ag.+HCG) group (32 patients)	P value		
Age (Year) (Mean ±SD).		29.49 ± 4.526	28.39 ± 3.6	28.53 ± 4.79	0.48		
BMI (kg/m²) (Mean ±SD).		29.8 ± 3.74	29.6 ± 5.44	28.4 ± 4.9	0.406		
Infertility type N (%)	1ry	39 (86.7%)	21 (67.7%)	26 (81.3%)	0.127		
	2ry	6 (13.3%)	10 (32.3%)	6 (18.8%)			
Infertility duration (year) (Mean ±SD).		5.8 ± 2.5	4.97 ± 2.36	4.9 ± 2.038	0.2		
Hormonal assay: (Mean ±SD).	FSH	4.84 ± 2.02	4.65 ± 1.89	8.38 ± 14.69	0.065		
	LH	8.1 ± 5.53	9.999 ± 4.96	9.04 ± 5.1	0.15		
	TSH	2.5 ± 1.9	2.18 ± 1.07	2.31 ± 1.38	0.815		
	Prolactin	13.4 ± 5.66	13.5 ± 4.6	13.7 ± 4.67	0.97		
	AMH	4.93 ± 3.56	5.36 ± 3.07	5.41 ± 3.88	0.728		
AFC by US in Day 2 of cycle (Mean ±SD).		32.8 ± 2.29	33.7 ± 2.7	34.03 ± 2.5	0.088		
Basic investigations: Semen Analysis N (%)	Normal	38 (84.4%)	30 (96.8%)	28 (87.5%)	P1 0.09	P2 0.2	P3 0.7
	Moderately affected	7 (15.6%)	1 (3.2%)	4 (12.5%)			
HSG N (%)	Normal	41 (91.1%)	29 (93.5%)	29 (90.6%)	P1 0.7	P2 0.7	P3 0.9
	Abnormal	4 (8.9%)	2 (6.5%)	3 (9.4%)			

Gyneco-logical surgery N (%)	LOD	+ve	13 (28.9%)	5 (16.1%)	3 (9.4%)	P1 0.6	P2 0.5	P3 0.2
		-ve	32 (71.1%)	26 (83.9%)	29 (90.6%)			
	Operative laparoscopy	+ve	13 (28.9%)	5 (16.1%)	3 (9.4%)	P1 0.6	P2 0.5	P3 0.2
		-ve	32 (71.1%)	26 (83.9%)	29 (90.6%)			

A P-value is deemed significant if it is ≤ 0.05. The percentages shown in the table represent within-group percentages. P1 denotes the P-value for the difference between the group that followed the Antagonist protocol with a GnRH Agonist trigger and the group that followed the Antagonist protocol with an hCG trigger. P2 denotes the P-value for the difference between the group that followed the Antagonist protocol with an hCG trigger and the group that followed the Long Agonist protocol with an hCG trigger. P3 denotes the P-value for the difference between the group that followed the Antagonist protocol with a GnRH Agonist trigger and the group that followed the Long Agonist protocol with an hCG trigger.

Our analysis revealed significant differences in estradiol (E2) levels on the trigger day among patients undergoing different IVF/ICSI protocols. Additionally, a complete blood count (CBC) analysis, including white blood cell (WBC) count, platelet count, and hematocrit, showed variations depending on the protocol. Similarly, serum glutamic oxaloacetic transaminase (SGOT) and creatinine levels, along with platelet count, exhibited protocol-dependent differences.

Various IVF/ICSI protocols showed no significant difference between groups in serum albumin, SGPT levels, the number of follicles >18mm (by US), or dominant follicle size (by US). To calculate a more accurate P-value using Fisher's exact test, a 2x2 data analysis was performed. The need for hospital admission and the presence of ascites (fluid buildup in the abdomen) were more common in the (Antagonist protocol with hCG trigger) and (Long agonist protocol with hCG trigger) groups, which exhibited statistically significant differences in both when compared with the (Antagonist protocol with GnRH agonist trigger) group (P1 and P3). However, there was no statistically significant difference between the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger in terms of hospital admission and ascites. (Table 3)

Table (3): Detailed OHSS data.

		(Ant.+Agonist trig.) group (45 patients)	(Ant.+HCG) group (31 patients)	(Long Ag.+HCG) group (32 patients)	P value		
Past history of OHSS N (%)	+ve	1 (2.2%)	0	0	P1 0.4	P2 -	P3 0.4
	-ve	44 (97.8%)	31 (100%)	32 (100%)			

OHSS grade	Moderate N (%)	1 (2.2%)	3 (9.68%)	3 (9.38%)	P1 0.3	P2 0.8	P30.3
	Severe N (%)	0	4 (12.9%)	5 (15.63%)			
Type of OHSS	Early N (%)	1 (2.2%)	3 (9.68%)	4 (12.5%)	P1 0.3	P2 0.8	P3 0.4
	Late N (%)	0	4 (12.9%)	4 (12.5%)			
Estradiol (E2) level at trigger day (Mean ±SD).		1966 ± 2405.8	2990 ± 2889.7	3069.5 ± 1393.8	0.001*		
Laboratory Investigations (Mean ±SD).	WBCs/ mm3	7679.8 ± 2797.6	12197 ± 7186.33	11231.5 ± 8089.9	0.003*		
	Hematocrit%	35.5 ± 4.5	41.6 ± 8.29	40.85 ± 8.99	0.001*		
	Serum albumin level mg/dl	4.3 ± 0.5	3.8 ± 1.37	3.6 ± 1.5	0.688		
	SGOT U/ml	22.5 ± 10.6	30.3 ± 15.5	31.6 ± 20.86	0.042*		
	SGPT U/ml	25.2 ± 5.4	41.4 ± 36.4	40.85 ± 36.35	0.331		
	Serum creatinine level mg/dl	0.86 ± 0.17	1.07 ± 0.35	1.07 ± 0.38	0.01*		
	Platelet count K/uL	286.6 ± 84.4	335.4 ± 95.7	334.15 ± 102.57	0.03*		
Ascites N (%)	Positive (+)	1 (2.2%)	7 (22.6%)	8 (25%)	P1 0.005*	P2 0.8	P3 0.002*
	Negative (-)	44 (97.8%)	24 (77.4%)	24 (75%)			
Ultrasound (Mean ±SD).	Number of follicles >18mm	11.93 ± 6.24	14.94 ± 7.52	14.22 ± 4.14	0.08		
	Dominant follicle size	19.51 ± 1.79	19.84 ± 2.07	19.88 ± 1.43	0.56		
Hospital Admission N (%)		1 (2.2%)	7 (22.6%)	8 (25%)	P1 0.005*	P2 0.8	P3 0.002*

*A P-value is deemed significant if it is ≤ 0.05. The percentages shown in the table represent within-group percentages. P1 denotes the P-value for the difference between the group that followed the Antagonist protocol with a GnRH Agonist trigger and the group that followed the Antagonist protocol with an hCG trigger. P2 denotes the P-value for the difference between the group that followed the Antagonist protocol with an hCG trigger and the group that followed the Long Agonist protocol with an hCG trigger. P3 denotes the P-value for the difference between the group that followed the Antagonist protocol with a GnRH Agonist trigger and the group that followed the Long Agonist protocol with an hCG trigger.

The number of oocytes retrieved significantly differed among patients undergoing different IVF/ICSI protocols. However, there was no statistically significant association between the IVF/ICSI protocol employed and the resulting number of embryos. Owing to the limited size of the sample, a Fisher's exact test, which requires a smaller sample size, was used. The type of pituitary suppression protocol and oocyte maturation triggers significantly impacted the choice between freezing all embryos and fresh transfer within different patient groups. This is likely due to varying OHSS risks and the effect of the trigger on endometrial receptivity. There was a difference that was statistically significant. when the group following the Antagonist protocol with a GnRH Agonist trigger was compared with either the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger regarding the number of transferred embryos of grade A (D3). (Table 4)

Table (4): Oocytes and embryo grading.

		(Ant.+Agonist trig.) group (45 patients)	(Ant.+HCG) group (31 patients)	(Long Ag.+HCG) group (32 patients)	P value		
The average number of oocytes collected (Mean ±SD).		19.2 ± 7.5	24.23 ± 10	31.7 ± 11.6	0.001*		
Number of embryos (Mean ±SD).		10.73 ± 5.29	11.19 ± 4.32	11.75 ± 4.18	0.73		
Freeze all N (%)	Yes	45 (100%)	8 (25.8%)	2 (6.3%)	P1 0.001*	P2 0.04*	P3 0.001*
	No	0	23 (74.2%)	30 (93.8%)			
Fresh embryo transfer N (%)	Yes	0	23 (74.2%)	31 (96.9%)	P1 0.001*	P2 0.011*	P3 0.001*
	No	45 (100%)	8 (25.8%)	1 (3.1%)			
Number of transferred embryos of grade A (D3) N (%)	0	45 (100%)	8 (25.8%)	2 (6.3%)	P1 0.001*	P2 0.9	P3 0.001*
	1	0	9 (29%)	15 (46.9%)			
	2	0	14 (45.2%)	14 (43.8%)			
	3	0	0	1 (3.1%)			

*A P-value is considered significant if it is ≤ 0.05. The percentages displayed in the table are within-group percentages. P1 represents the P-value for the difference between the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Antagonist protocol with an hCG trigger, P2 represents the P-value for the difference between the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger, and P3 represents the P-value for the difference between the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Long Agonist

protocol with an hCG trigger. The P-value of the "number of transferred embryos" was calculated using a 2x2 analysis comparing two groups: one with zero or one embryo and the other with more than one embryo.

There wasn't significant statistical link between the type of pituitary suppression protocol, whether antagonist or agonist, and the pregnancy rates following IVF/ICSI procedures. (Table 5)

Table (5): Pregnancy data.

N(%)		(Ant.+HCG) group (31 patients) Antagonist protocol	(Long Ag.+HCG) group (32 patients) Agonist protocol	P value by Fisher's exact test
Chemical pregnancy	Yes	8 (25.8%)	4 (12.5%)	0.182
	No	23 (74.2%)	28 (87.5%)	
Clinical pregnancy	Yes	8 (25.8%)	4 (12.5%)	0.182
	No	23 (74.2%)	28 (87.5%)	
Ongoing clinical pregnancy (Viable)	Yes	8 (25.8%)	4 (12.5%)	0.182
	No	23 (74.2%)	28 (87.5%)	
Multiple pregnancy	Yes	2 (6.5%)	3 (9.4%)	0.67
	No	29 (93.5%)	29 (90.6%)	

The group following the Antagonist protocol with a GnRH Agonist trigger was excluded from the analysis of pregnancy data because all patients in this group underwent freezing of all embryos. A P-value is considered significant if it is ≤ 0.05. The percentages displayed in the table are within-group percentages.

The analysis of OHSS patients revealed a distinct difference between moderate and severe cases. Notably, all severe cases presented with ascites and pleural effusion, while only one case experienced blood clot issues. The management approach significantly differed; all severe cases required paracentesis, anticoagulation, and intensive care, compared to the moderate group where these interventions were used in a limited manner. (Table 6)

Table (6): incidence of symptoms, signs and management modalities of OHSS according to its grade.

N (%)	Moderate OHSS	Severe OHSS	
Thromboembolic events	(7 patients)	(9 patients)	P value
Ascites	0	1 (11.1%)	0.56
Pleural effusion	7 (100%)	9 (100%)	-
Coagulation abnormalities	0	9 (100%)	0.01*
Multiple system failure	0	1 (11.1%)	0.56
Renal shut down	0	0	-
Paracentesis	0	0	-
LMW heparin	1(14.3%)	9 (100%)	0.001*
Intensive critical care	7 (100%)	9 (100%)	-
Albumin administration	0	9 (100%)	0.01*
	7 (100%)	9 (100%)	-

The table presents the percentage of patients in each grade of OHSS. A P-value is considered significant if it is ≤ 0.05.

The potential risk factors for Ovarian Hyperstimulation Syndrome (OHSS) was investigated by comparing baseline characteristics, ovarian reserve markers, stimulation parameters, oocyte retrieval data, and cycle outcomes between patients who developed OHSS and those who did not. Baseline characteristics included age, body mass index (BMI), and duration of infertility. The ovarian reserve markers assessed were the antral follicle count (AFC) by ultrasound on cycle day 2 and the Anti-Müllerian Hormone (AMH) level. The history of laparoscopic ovarian drilling (LOD) was also taken into account. The stimulation parameter analyzed was the estradiol (E2) level on the trigger day for oocyte retrieval. Data on number of follicles exceeding 18mm, the number of oocytes collected, and cycle outcomes such as freeze-all cycles, fresh embryo transfers, rates of clinical pregnancy, multiple pregnancy rates, and the number of transferred embryos of high quality (grade A, Day 3) were also compared. All these factors showed significant differences between patients who experienced OHSS and those who didn't. (Table 7)

Table (7): Factors affecting OHSS incidence significantly.

Age (Year) (Mean ±SD).		26.13 ± 2.09	29.37 ± 4.47	0.005*
BMI (kg/m²) (Mean ±SD).		23 ± 1.5	30.4 ± 4	0.001*
Infertility duration (years) (Mean ±SD).		3.44 ± 0.73	5.63 ± 2.4	0.001*
AFC by US in Day 2 of cycle (Mean ±SD).		35.75 ± 2.4	33 ± 2.3	0.001*
AMH (Mean ±SD).		11.05 ± 2.7	4.18 ± 2.48	0.001*
LOD N (%).		0	21 (22.8%)	0.034*
Estradiol (E2) level at trigger day (Mean ±SD).		6760 ± 3646	1861 ± 868.8	0.001*
Number of follicles >18mm (Mean ±SD).		20.44 ± 6.15	12.26 ± 5.4	0.001*
Number of oocytes retrieved (Mean ±SD).		44.25 ± 9.7	20.89 ± 6.5	0.001*
Freeze all N (%).		4 (25%)	51 (55.4%)	0.025*
Fresh embryo transfer N (%).		12 (75%)	42 (45.7%)	0.03*
Clinical pregnancy (+ve) N (%).		8 (50%)	4 (4.3%)	0.001*
Multiple pregnancy N (%).		5 (31.3%)	0	0.001*
Number of transferred embryos of grade A (D3) N (%).	Zero or one embryo transferred	8 (50%)	71 (77.2%)	0.024*
	More than one embryo transferred	8 (50%)	21 (22.8%)	

*A P-value is considered significant if it is ≤ 0.05. The percentage displayed in the table pertains to OHSS.

Discussion

This retrospective study investigated the impact of ovarian stimulation protocols and oocyte maturation triggers on the incidence and intensity of OHSS in 108 PCOS patients who underwent IVF/ICSI. The antagonist protocol with a GnRH agonist trigger had the lowest incidence of OHSS (2.2%, moderate only) with zero incidence of severe or lethal grades, while the long agonist protocol with an hCG trigger had the highest (25%, including both moderate and severe grades). There was a significant difference between the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Long Agonist protocol with an hCG trigger. Also, the group following the Antagonist protocol with a GnRH Agonist trigger and the group following the Antagonist protocol with an hCG trigger showed significant differences, despite having the same pituitary suppression protocol (antagonist). The highest incidence was in the group triggered by hCG. There was no significant disparity between the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger despite the difference in pituitary suppression protocol (antagonist vs long agonist), but both were triggered by hCG. This suggests that the Antagonist protocol is a powerful preventive measure against OHSS in PCOS patients if oocyte maturation is triggered by a GnRH agonist, segmentation (freeze all) is practiced, and hCG is avoided. These findings align with those found in the literature by (6, 8-11).

The GnRH antagonist protocol is emerging as the preferred approach for PCOS patients due to its potential to reduce the risk of OHSS, its financial viability, and its shorter duration of stimulation, all without negatively affecting the likelihood of pregnancy outcomes (12). The present study supports this, demonstrating a lower incidence of OHSS with the antagonist protocol, especially when oocyte maturation was achieved by GnRH agonist instead of hCG. This aligns with practices aimed at removing the possibility of severe OHSS (13). Overall, the GnRH antagonist protocol is advised for patients with a high likelihood of OHSS, and substituting hCG with a GnRH agonist can further decrease the risk of severe OHSS (14).

The current study discovered that using hCG as an oocyte maturation trigger increased the likelihood of OHSS in PCOS patients undergoing IVF/ICSI. This finding aligns with the literature, which reports an association between hCG and an increased risk of OHSS (15, 16).

The current study found no difference of significance in age and BMI among patients undergoing different IVF/ICSI protocols, suggesting that age and BMI might not be a primary factor in the selection of the protocol. However, a difference that was significant in age and BMI was observed among patients who developed OHSS and those who did not. A young age, specifically ≤ 28 years, increased the incidence of OHSS. This aligns with existing literature, where a younger age is identified as a contributing factor for OHSS, regardless of the specific IVF/ICSI protocol used (17, 18). The presence of OHSS revealed a potential association with an ideal BMI. While this study and others (19) observed a trend towards a lower BMI in patients with OHSS, the existing literature is not entirely consistent. (17) identified a low BMI as a risk factor for OHSS, while (20) reported no such correlation. Further study is required to clarify the connection between BMI and the risk of OHSS.

AMH emerged as a risk factor for OHSS, with levels equal to or exceeding 8.5 ng/mL associated with a higher incidence. This aligns with existing research suggesting that extremely high AMH levels (>50 pmol/L)

increase the risk of OHSS in PCOS patients in comparison to lower AMH levels (21). AMH appears to be a more reliable Indicator of ovarian response and OHSS than either age or BMI, allowing for tailored strategies to minimize the risk of overstimulation in patients with elevated AMH (22, 23).

While the Antral Follicle Count (AFC) assessed via ultrasound on the second day of a cycle didn't significantly vary between patients who underwent different IVF/ICSI protocols, it became a risk factor for OHSS when it reached or exceeded 35. This aligns with the observation that patients who experienced OHSS tended to have a higher AFC compared to those who didn't. Studies have suggested different thresholds for predicting OHSS using AFC and other markers: (24) proposed 19.5 for AFC, 22.5 pmol/L for AMH, and 9.5 for the number of collected eggs. On the other hand, (19) reported that an AFC of 24 or higher was found to be a risk factor for moderate-to-severe ovarian hyperstimulation syndrome (OHSS) in patients with polycystic ovary syndrome (PCOS). These findings suggest that AFC can help predict OHSS. Therefore, knowing a patient's AFC levels is crucial for planning and managing the risks of OHSS during fertility treatments.

Laparoscopic ovarian drilling (LOD) seemed to be protective against OHSS, particularly in patients with PCOS. Studies like (25) suggested that a history of LOD significantly diminishes the risk of OHSS in this population. Compared to traditional gonadotropin therapy for ovulation induction, LOD offers similar results but avoids the side effects of OHSS (26).

Estradiol levels, measured on the day of ovulation trigger, significantly differed among patients undergoing various IVF/ICSI protocols. Protocols associated with a higher incidence of OHSS resulted in demonstrably elevated E2 levels within those groups. This aligns with findings from (18, 27, 28), who all reported a strong correlation between high E2 levels and OHSS development. Our study identified a high risk of OHSS in PCOS patients with E2 levels of ≥ 3500 pg/mL on the trigger day, suggesting a potential risk threshold. However, it is important to consider variations across studies. For instance, (29) proposed a cut-off of ≥5000 pg/mL, while (18) used a broader range of 3000-5000 pg/mL on the trigger day. Additionally, (27) identified E2 levels exceeding 126 ng/mL on Day 3 of the cycle and a significant fold increase by Day 10 as potential risk factors. These findings collectively suggest that E2 level can be a valuable predictor of OHSS. However, the specific cut-off value for high risk may vary depending on the study population and the specific IVF/ICSI protocol used.

In our study, it was found that having ≥ 15 follicles with a diameter exceeding 18 mm was linked to a heightened risk of OHSS in PCOS cases. On the other hand, the number of follicles > 18mm and the dominant follicle size didn't show any difference of significance between the IVF/ICSI protocol groups. Measuring follicles before retrieval can predict OHSS risk, with ≥13 follicles ≥11 mm in diameter (30). Throughout ovulation stimulation, a notably greater quantity of follicles was observed in the patient group experiencing OHSS (31).

In the present study, having ≥ 28 oocytes retrieved was recognized as a factor of risk for OHSS in PCOS cases. The study also revealed a difference with significance between groups of IVF/ICSI protocols. (27) found that AFC and the count of eggs retrieved were indicative of OHSS, with women who developed OHSS yielding a higher number of eggs per cycle. Additionally, the ideal number of oocytes retrieved is 24, and it is recommended to freeze all embryos if 25 or more oocytes are retrieved to avoid late onset OHSS (32).

Clinical pregnancy, when it occurred in PCOS cases undergoing IVF/ICSI, increased OHSS risk. Pregnancy itself is a known risk

contributor to OHSS, particularly late-onset OHSS, which typically develops 10-17 days post-treatment (22, 33). This is because rising hCG levels from pregnancy can exacerbate existing early OHSS or trigger late-onset OHSS (18). To mitigate this risk, the freeze-all approach, in which embryos are frozen and transferred in a separate cycle, can be considered to decouple pregnancy from the initial ovarian stimulation phase (34).

Freezing all embryos (the freeze-all strategy) as opposed to transferring fresh embryos appeared to be a valuable tool to lower the risk of OHSS in PCOS patients undergoing IVF/ICSI. Our investigation revealed a statistically significant relationship between the choice of oocyte maturation trigger (hCG versus GnRH agonist) and the preferred embryo transfer strategy within the antagonist protocol. Notably, patients triggered with the GnRH agonist exclusively underwent a freeze-all approach, while those triggered with hCG demonstrated a greater preference towards fresh embryo transfer. Studies have shown that compared to fresh embryo transfer, the freeze-all approach significantly reduces the risk of OHSS development while maintaining elevated rates of live births in following frozen embryo transfer cycles (35, 36). This benefit is particularly important for patients at high risk of OHSS, and the freeze-all strategy can be safely carried out using a GnRH agonist trigger (36). Furthermore, some studies suggest the freeze-all approach might even improve pregnancy rates beyond just reducing OHSS risk (35). Therefore, considering a freeze-all technique, especially when fresh embryo transfer carries a high OHSS risk, presents a valuable alternative (37).

The present study has shown that multiple pregnancies have a connection with an increased risk of OHSS, particularly the more severe form. For instance, twin pregnancies exhibit a higher tendency towards severe OHSS compared to mild or moderate forms, and the incidence of late-onset OHSS is more than double that of early-onset OHSS (38, 39).

The present study revealed a statistically significant difference in the number of transferred high-quality (Grade A, D3) embryos among patient groups with different oocyte maturation triggers. Patients triggered with the GnRH agonist exclusively underwent a freeze-all strategy, indicating no transfers of these embryos. Conversely, the hCG-triggered groups (the group following the Antagonist protocol with an hCG trigger and the group following the Long Agonist protocol with an hCG trigger) exhibited a distribution of > 50% receiving either one embryo or undergoing a freeze-all, while the remaining < 50% received more than one embryo transfer. The analysis identified the number of transferred embryos of grade A (D3) if > 1 as a risk factor for OHSS. Individuals with a higher number of transferred embryos exhibited a greater likelihood of experiencing severe OHSS (40).

Conclusion

In conclusion, the cases described highlight the potential risks associated with OHSS in patients with PCOS who are undergoing treatment with IVF/ICSI. To reduce the risk of OHSS, certain measures can be taken, including the use of antagonist protocol or GnRH agonist trigger for ovulation, as well as cryopreservation of all embryos. It is important for healthcare providers to closely monitor patients with PCOS during IVF/ICSI and individualize treatment plans to lower the risk of OHSS incidence and associated complications.

Conflict of interest: None exists.

Funding: This research did not receive any specific grant from funding bodies.

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