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Original Article

Polycystic Ovary Syndrome Develops the Complications of Assisted Reproductive Technologies

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a serious complication that remains a threat to every patient experiencing stimulation of ovulation. Polycystic ovary syndrome (PCOS) appears to be the most important predisposing factor for OHSS. The severity of OHSS is associated with the degree of the follicular response to the ovulation inducing agents. The objective of this study was to investigate the relationship between PCOS with the risk of moderate-to-severe OHSS in intracytoplasmic sperm injection treatment patients. Sixty patients in the reproductive ages (20-38), including OHSS patients and age-matched normoresponders were included in this study. Patients who had larger follicle counts on the day of hCG injection were considered at risk for developing moderate-to-severe OHSS. In addition, oocyte quality was assessed about 20-30 min after oocyte pickup. The incidence of OHSS in PCOS patients increased significantly up to 13.9 times higher than in patients without PCOS (*OR*=13.900; *P*=0.007). Moreover, moderate-to-severe OHSS increased significantly (*OR*=3.860; *P*=0.043) in patients with primary infertility than those with secondary infertility. In addition, oocyte quality was not affected with the severity of OHSS. In conclusion, the risk of moderate-to-severe OHSS is correlated with PCOS and primary infertility without affecting oocyte quality.

Keywords: Polycystic ovary syndrome, Ovarian hyperstimulation syndrome, Assisted reproductive technologies, Intracytoplasmic sperm injection

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of infertility treatment with assisted reproductive technologies (1). The syndrome may become lethal due to several complications including thromboembolism, compromised pulmonary and cardiovascular function, accumulation of fluids in the peritoneal cavity, respiratory distress, oliguria, and acute renal failure (1-3). The severity of OHSS is associated with the degree of the follicular response to the ovulation (4) and with higher follicle count (5).

According to previous investigations, polycystic ovary syndrome (PCOS) is an endocrine disorder that appears to be the most important predisposing factor for OHSS (6-8). PCOS is thought to be the most common cause of anovulatory infertility as well as anovulatory disturbances (9). It is characterized by poor oocyte quality and reduced top-quality embryo

percentage, especially when it coincides with metabolic syndrome (10). A typical feature of polycystic ovaries is extreme androgen biosynthesis causing excess follicles and elevation of theca interna and granulosa cells proliferation (11).

Traditionally, the superlative approaches for predicting OHSS arising are increased estradiol (E_2) concentrations on the day of human chorionic gonadotropin (hCG) injection (E_2>3 000 pg/mL), elevated ovarian response, history of OHSS, PCOS, small follicles count, and the retrieved oocytes count (7, 8). Papanikolaou, Pozzobon (12) proposed that the high count of larger follicles (medium/large follicles ≥ 13 follicles; ≥ 11 mm in diameter) is the threshold of OHSS risk with a sensitivity of 84.9% and specificity of 69.0%. While the low number of follicles (<13) was correlated with a highly significant negative likelihood for developing OHSS (12). Therefore, we selected larger (medium/large) follicles count on the day of hCG injection in our study to classify OHSS.

As mentioned above, OHSS continues to be a serious complication of assisted reproductive techniques. However, studies about the correlation between risk factors and the severity of OHSS in PCOS patients are rare and still unclear (13). We hypothesized that some factors including PCOS may be correlated to the risk of OHSS. Thus it is necessary to prevent risk of OHSS due to these factors and thereby increase the efficacy of assisted reproductive techniques. This study aimed to investigate the possible correlation between PCOS, and some demographics of patients such as superovulation protocol and infertility type with the incidence and risk of OHSS in ICSI patients. In addition, to examine whether oocyte quality is affected by this syndrome.

2. Materials and Methods

Sixty patients in the reproductive ages (20-38 years) with female causes of infertility were recruited in this study. They were 41 women suffering from OHSS (moderate-to-severe OHSS) with or without PCOS. In addition, 19 age-matched normoresponders were entered in this study. They all underwent controlled ovarian hyperstimulation with gonadotropin releasing hormone (GnRH) protocols of intracytoplasmic sperm injection (ICSI). Primary infertility was defined as failure to conceive (never pregnant) following one year of consistent, unprotected intercourse, whereas secondary infertility was defined as incapability to achieve gestation after having previously delivered an infant without the use of infertility treatment (14). Forty five patients (75%) had primary infertility and the other fifteen patients (25%) had secondary infertility. Thirty-three patients (55%) underwent their first ICSI attempt and twenty-seven patients (45%) had two or more ICSI attempts. To avoid the possible effect of body weight on the incidence of OHSS and PCOS, patients with body mass index (BMI) ≥28 kg/m^2 were excluded from the study. In addition, patients aged ≥39 years old, diabetic, and endometriosis patients were excluded. All patients included in the study had no hypertension nor hepatic dysfunctions. Furthermore, the number of the previous IVF/ICSI tries, duration of infertility, history of previous OHSS, and endometrial thickness of all patients were recorded.

Twenty-five patients (41.7%) were daily administered with agonist long recombinant FSH (Gonal-F; Merk Serono, Germany). The other 35 patients (58.3%) were administered antagonist drugs daily (Cetrotide; Merk Serono, Germany). In all patients, hCG (Pregnyl; IBSA, the Netherlands) was used to stimulate the final oocyte maturation. Follicles were monitored regularly, their number and size were recorded using ultrasonography. Follicles with a small size were smaller than 11 mm, medium sized follicles ranged between 11 and 15 mm, and the follicles larger or equal to 16 were grouped within the large sized ones. The oocyte pickup was achieved about 36-38 h following hCG intramuscular injection. Oocyte quality were directly assessed about 20-30 min after oocyte collection; the top quality oocytes were metaphase II (MII) stage according to their stage of division under microscope.

The diagnostic criteria of PCOS were according to criteria of Rotterdam (15) by ultrasonography. The

presence of 12 or more follicles in either ovary with the size of 2-9 mm in diameter, and/or increased ovarian volume ≥ 10 mL.

The classification of OHSS in the patients at risk of moderate-to-severe OHSS was achieved according to Papanikolaou, Pozzobon (12). We used the same approach in classification of OHSS in our previous paper (16). Briefly, we explored threshold of larger (medium/large) follicles count ≥ 18 follicles with ≥ 11 mm diameter in high risk for moderate-to-severe OHSS, 13-18 follicles with ≥ 11 mm diameter in low risk for moderate-to-severe OHSS, whereas larger follicles count of less than 13 follicles on the day of hCG injection were classified as normoresponders.

Comparisons of outcomes among the three groups of the study were done using Kruskal-Wallis test. Regarding variables with significant differences, comparison (2×2) groups were performed using Mann-Whitney test with the correction of Benferroni. To select those explanatory variables that best explained the chance of OHSS, ordinal logistic regression was used. At the first step, explanatory variables including: PCOS, infertility type, superovulation protocol, and history of previous IVF/ICSI were entered in the model as categorical variables. Also, age and duration of infertility were entered in the model as quantitative variables. To select those explanatory variables that best explained the chance of OHSS, backward stepwise approach was used. The significance of each explanatory variable in the model was tested using the Wald test. Explanatory variables that were not statistically significant were removed from the model one at a time, beginning with the least significant, until the estimated regression coefficients for all retained variables were significant at a level of $P<0.05$.

3. Results

The characteristics of the patients enrolled in this study are presented in table 1. Embryo transfer was done in 75% (45/60) and canceled in 25% (15/60) of patients. The age, infertility period, superovulation protocol and the number of previous IVF/ICSI attempts did not associate significantly with the risk of OHSS, while the risk of moderate-to- sever OHSS was increased significantly ([OR = 3.86; 95%CI:1.04-14.29]; P=0.043) in patients with primary infertility than those with secondary infertility.

The number of oocytes retrieved was significantly different between normoresponders and OHSS groups. Oocytes number was significantly higher in both OHSS groups than normoresponders (P=0.001), whereas the number of oocytes between the two OHSS groups did not differ significantly (P=0.151) （Table 2）.

Table 1. Patients and ICSI cycles characteristics of the three groups of the study

	Normoresponders	**Low-risk OHSS**	**High-risk OHSS**	***P* value**
Number of patients	19	13	28	-
Female age (year)	32.11 (20-38)	29.0 (23-35)	29.46 (23-38)	NS
PCOS				
Yes n (%)	0 (0)	3 (5)	7 (11.6)	0.007
No n (%)	19 (31.7)	10 (16.7)	21 (35)	
Infertility type				
Primary n (%)	12 (20)	9 (15)	24 (40)	0.043
Secondary n (%)	7 (11.6)	4 (6.7)	4 (6.7)	
Duration of infertility (year)	4.89 (1-16)	5.96 (0.5-14)	6.04 (1-13)	NS
Embryo transfer				
Achieved n (%)	14 (23.4)	13 (21.6)	18 (30)	NS
Canceled n (%)	5 (8.3)	0 (0)	10 (16.7)	

Variables are presented as frequency (%). Quantitative variables are presented as median (minimum-maximum). The chance of moderate-to-severe OHSS in high risk OHSS group increased in PCOS patients up to 13.9 times higher than other patients without PCOS. OHSS is higher in patients with primary infertility than those with secondary infertility. Differences are statistically significant ($p<0.05$). NS; no significant differences. PCOS; polycystic ovarian syndrome.

Table 2. Description of follicles assessment and oocyte quality in three groups of the study. Variables were presented as median (Q1£-Q3¥)

	Normoresponders	Low-risk OHSS	High-risk OHSS
Number of patients	19	13	28
Number of follicles	10 (6-12)[a]	15 (15-17)[b]	25 (20-39)[b]
Large follicles %	0.42 (0.23-0.53)	0.53 (0.33-0.62)	0.37 (0.23-0.63)
Medium follicles %	0.38 (0.16-0.53)	0.41 (0.23-0.50)	0.44 (0.28-0.56)
Small follicles %	0.17 (0.00-0.36)	0.00 (0.00-0.13)	0.13 (0.00-0.30)
Number of oocytes	6.0 (4.5-7.5)[a]	11.0 (9-13)[b]	13.5 (9-20)[b]
Top quality oocytes (Metaphase II) oocytes (%)	1.00 (1.00 -1.00)	1.00 (0.86-1.00)	1.00 (0.86-1.00)
Germinal vesicles oocytes (%)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Necrotic oocytes retrieved (%)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.11)

£ First quartile
¥ Third quartile
[ab] Values within a row followed by different superscript letters are significantly different

Other parameters including follicles size (small, medium, and large follicles percentage), oocyte quality (top quality oocytes or MII, germinal vesicle, and necrotic oocytes percentage) did not show significant differences between normoresponders, low risk and high-risk OHSS groups. The number of follicles was significantly different between the three groups of the study and higher in both OHSS groups than normoresponders (P=0.001) (Table 2).

4. Discussion

The present study revealed that the severity of OHSS increased in PCOS patients especially when they had primary infertility. Furthermore, oocyte quality was not affected with the severity of OHSS.

Kahnberg, Enskog (17) proposed in their prospective observational study that the number of larger follicles was considered the only independent predictor of OHSS with a sensitivity of 82.1% and specificity of 79.4%. Delvigne (18) suggested that follicles number ≥ 13 (11 mm diameter) and oocytes retrieved ≥ 20 are additional alarm signs for OHSS. Griesinger, Verweij (19) recommended that the number of follicles on the day of hCG can classify the patients as being at risk for developing of OHSS on the day of hCG with an optimal threshold of ≥ 19 follicles ≥ 11mm diameter. In addition, follicles number on this day was correlated with an increased risk for severe and moderate-to-severe OHSS, whereas E_2 concentration was less reliable for expectation of a syndrome. Recently, Schirmer, Kulkarni (20) concluded from their large retrospective cohort study from 2000 to 2015 that the number retrieved oocytes is a modifiable predictor factor for OHSS predicting.

In our patients, OHSS in PCOS patients was significantly higher. As mentioned before, PCOS appears to be the major risk factor for OHSS incidence. As the most common endocrine disorder, PCOS is a clear risk factor for OHSS in reproductive age women. However, the precise etiology of OHSS in PCOS patients is still unclear and its accurate expectation in an individual IVF/ICSI cycle is problematic (21). Costello, Chew (22) suggested an altered folliculogenesis as one of the main characteristics of polycystic ovaries. Raised luteinizing hormone concentrations in PCOS patients might be the cause of an elevated vascular endothelial growth factor (VEGF) bioactivity, which, in turn, motivates a rich vascularity and appearance of the clinical sings of PCOS (22).

Our results revealed that OHSS incidence in patients with primary infertility was higher (75%) than those with secondary type of infertility (25%). The mean duration of infertility was (5.96 y) in patients with a low-risk of OHSS, and (5.82 y) in high-risk OHSS patients. Our results were consistent with the results of previous retrospective studies (14, 23) and case reports (24, 25). Xu, Zhou (14) found a similar distribution of OHSS to our study with 61.6 % of their OHSS patients with primary infertility and the other 38.4% with secondary infertility. Ashrafi, Bahmanabadi (23)

showed that 96.5% of their patients have primary infertility and 3.5% secondary infertility. Furthermore, OHSS was also recorded in case reports of patients with primary infertility (23). Therefore, we might consider the primary type of infertility as an additional risk factor for predicting moderate-to-severe OHSS.

Several metabolic alterations hypothetically influence oocyte quality, irrespective of the patient's BMI (26). The inflammatory status in OHSS patients may affect the microenvironment of the oocyte and declines oocyte quality, two-pronuclear (2PN) fertility rate, top quality embryo rate and available embryo rate (27). When cycles are handled with assisted reproductive interventions to induce ovulation, the interval of pro-estrus, ovulatory follicle growth rate and ovulatory follicle size are factors that distress the follicular and oocyte development (28). However, our study revealed no significant effect of moderate-to-severe OHSS on oocyte quality, although the number of follicles and oocytes in both OHSS groups were significantly higher than in normoresponders.

There are, however, some imitations to this study. The PCOS patients were younger compared to the other patients without PCOS. This finding is due to the fact that the number of ovarian follicles decreases with age (18). Furthermore, the present study was part of a larger research project and the sample size was not determined for this study. We found 19 normoresponder and 41 OHSS (13 low-risk and 28 high-risk) patients during our investigation. Therefore, power of test might be insufficient when we accept null hypothesis (lack of significant association) because of small sample size.

In conclusion, the present study has shown that the severity of OHSS can override when the same patient has PCOS with primary infertility. The oocyte quality was not affected with OHSS, both in patients at low-risk and high-risk of OHSS. Thus, further studies in future should be designed to explain the precise mechanism by which PCOS acts to develop the severity of OHSS.

Authors' Contribution

M. J. A. and A. P. conceptualized and designed the study, interpreted the results and drafted the paper; A. A. contributed in sampling and analyzing data, M. Am. categorized patients and collected F. F. samples, M. Az. analyzed data. All authors read and approved the final manuscript.

Ethics

The study was approved by Ethical Committee of Ferdowsi University of Mashhad & Mashhad University of Medical Sciences, Mashhad, Iran (Project approval number 3/43276).

Conflict of Interest

The authors declare that they have no conflict of interest.

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