Predictive Factors Associated with Ovarian Hyperstimulation Syndrome in Indonesian Women Undergoing IVF

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Abstract

Background: In line with the increasing practice of in-vitro fertilization, it is crucial to pay attention onits complications. The most common iatrogenic complication of assisted reproductive technologies (ART) is ovarian hyperstimulation syndrome (OHSS). Several characteristics are useful in identifying high-risk patients in order to prevent OHSS.

Method: This study analysed characteristics of age, body mass index (BMI), antral follicle count (AFC), estradiol levels, and the number of oocytes between two unpaired groups of 20 women with OHSS and 19 women, who did not experience OHSS.

Results: The characteristics of AFC ($p = 0.012$), estradiol levels ($p < 0.001$), and the number of oocytes ($p < 0.001$) showed were significantly different between the two groups. Women with higher AFC were more likely to have OHSS, with OR of 3.33 (95% CI 0.77–14.31). Additionally, women with higher levels of estradiol and number of oocytes were also more likely to have OHSS, OR 76.5 (95% CI 9.66–605.67) and 81 (95% CI 4.2–1561.6), respectively. Other patient's characteristics did not differ significantly ($p > 0.05$).

Conclusions: Women with AFC above ten follicles, estradiol levels above 3000 pg/ml, and oocytes count of more than 12 were more likely to develop OHSS.

Keywords: *OHSS, IVF, prediction, prevention, risk factors.*

Introduction

A continued increase of clinics and treatment cycles of assisted reproductive technology (ART) has been globally reported by the International Committee Monitoring Assisted Reproductive Technologies (ICMART) [1] An ART's procedure, which is known as controlled ovarian stimulation (COS), induces multiple follicular selection, codominance, and ovulation by deliberately administering pharmacological therapy.[2] The procedure may lead to a potentially life-threatening complication of ovarian hyperstimulation, namely ovarian hyperstimulation syndrome (OHSS).[3] The clinical manifestations of OHSS are a consequence of an increase in vascular permeability, which results in the accumulation of fluid in the abdomen and other body cavities, haemoconcentration, and reduced blood perfusion.[4] Ovarian hyperstimulation syndrome often occurs during in-vitro fertilization (IVF) cycle and believes to be closely related to the administration of hCG.[5] It is hypothesized that hCG induces the release of a potent mediator that is responsible for the pathophysiology and clinical consequences of OHSS by directly affecting the vascular system.[4] This iatrogenic complication is considered a rare condition with a reported frequency of 1.2% of all cycles. [1]

Some studies reported several characteristics were

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determined as risk factors or OHSS prediction factors. According to Humaidan et al.,[6] risk factors/predictive factors are divided into primary and secondary factors. The primary factors are patient-related, such as young age, high basal anti-Müllerian hormone (AMH), previous history of OHSS, high antral follicles (antral follicle count or AFC), and PCOS (polycystic ovaries syndrome) or isolated PCOS. The secondary factors are associated with the ovarian response, including the number of follicles (on the day of hCG), increased levels of estradiol, vascular endothelial growth factor (VEGF), and inhibin-B. These factors were then adapted in another review, with the addition of more variables; a high oocytes count, hCG administration in the luteal phase support, and pregnancy as secondary predictive factors of OHSS. [3] Some studies also described a positive correlation of an asthenic habitus or a low BMI (body mass index) to have a high risk of developing OHSS. [2,7]

To date, OHSS has no definitive therapy, therefore prevention is a crucial step in the management of women with OHSS. Risk factors/predictive factors are expected to help in identifying high-risk patients, so that prevention of OHSS can be done as early as possible. Given so, the aims of this study are to determine the risk factors of OHSS. This study reviewed OHSS cases visiting the first referral hospital in East Java, the Dr. Soetomo General Hospital Surabaya. The characteristics of this group were then compared with women who did not develop OHSS of women undergoing IVF over a two-year study period.

Method

Data were collected from medical records of women who underwent IVF in the Graha Amerta Fertility Clinic Dr. Soetomo General Hospital from June 2017 to June 2019. Women who experienced OHSS were all included in this study as the case (OHSS) group, while women, who did not develop OHSS during the study period were included as the control (non-OHSS) group. The subjects' data on age, BMI, AFC, the clinical onset of OHSS, estradiol levels when hCG was administered, and the number of oocytes were obtained and analyzed. In addition, this study also compared the pregnancy outcome of the two groups. Ethical clearance was granted by the Health Research Ethics Committee Faculty of Medicine Universitas Airlangga. (1472/KEPK/Ix/2019)

Using the Kolmogorov-Smirnov normality test, most of the data were not normally distributed. Thus, to compare the two groups, the Chi-square Test, Fisher's Exact Test, and the nonparametric Mann-Whitney U Test were performed, when appropriate. Statistical significance were determined if $p < 0,05$.

Results

During the study period, there were 440 medical records and 39 of them were eligible for the study. Then the subjects were sorted into two groups, which were OHSS and non-OHSS groups, which included 20 and 19 subjects, respectively. In the OHSS group, there were 9 subjects who experienced early OHSS (60%), and 6 subjects experienced late OHSS (40%). In this study, early OHSS was defined if the onset of symptoms were within 9 days after hCG injection and late OHSS if symptoms occurred more than 9 days. Concerning the severity of the symptoms, most of the subjects (16 subjects, 84.2%) experienced mild OHSS. Only one subject had moderate OHSS manifesting as ascites and 2 subjects had severe OHSS of a pleural effusion. To determine the severity of OHSS, this study employed the classification adapted by Pfeifer et al. [7]

Table I presents data concerning pregnancy outcomes from both groups. Most subjects in the OHSS experienced a clinical and single pregnancy, 12 and 7 subjects, respectively. However, this result did not show a significant difference between the two groups. Clinical pregnancy was determined by the level of ß-hCG results exceeding 25 IU.

Table I. Pregnancy Outcomes

Characteristics	OHSS group (n = 20)		Non-OHSS group (n =19)		P value
	n	%	n	%	
Clinical Pregnancy					0.175
Pregnant	12	66.7%	6	37.5%	
Pregnancy Outcome					0,486
Single	7	77.8%	6	100%	
Triplets	2	22.2%	0	0%	

We found that a high AFC (> 10), estradiol level (> 3000), and oocyte count (>12) were significantly different between the two groups (Table II). The data also shows that these variables were associated with an increased risk of OHSS (Table III).

Table II. Characteristics associated with the development of OHSS

Characteristics	OHSS group (n = 20)		Non-OHSS group (n =19		P value
	n	%	n	%	
Age (years)	31.85 ± 3.52		34.47 ± 4.07		0.117
< 30	6	30%	4	21,1%	
30 – 35	12	60%	8	42.1%	
> 35	2	10%	7	36.8%	
BMI (kg/m2)	24.05 (19.5 – 37.5)		24 ± 3.11		0.168
18.7 – 24.9	7	50%	13	68.4%	
25 – 29.9	3	21.4%	5	26.3%	
≥ 30	4	28.6%	1	5.3%	
AFC	10 (6 – 20)		7.42 ± 4.05		0.012
< 5	0	0%	7	36.8%	
5 – 10	9	52.9%	8	42.1%	
> 10	8	47.1%	4	21.1%	
E2 on the day of hCG (pg/ml)					<0.001
< 2000	2	10%	9	47.4%	
2000 – 3000	0	0%	8	42.1%	
> 3000	18	90%	2	10.5%	
Number of Oocytes	14 (4 – 28)		4 (2 – 12)		< 0.001
< 8	3	15.8%	14	73.7%	
8 – 12	3	15.8%	5	26.3%	
> 12	13	68.4%	0	0%	

BMI : Body Mass Index; E2: Estradiol; AFC : Antral Follicle Count.

Table III. Odds ratio analysis of characteristics with an increased risk of OHSS

Characteristics	OHSS group (n = 20)		Non-OHSS group (n = 20)		OR	95% CI
	n	%	n	%		
AFC					3.33	(0.77–14.31)
<10	9	52.9%	15	78.9%		
>10	8	47.1%	4	21.1%		
E2 on the day of hCG (pg/ml)					76.5	(9.66–605.67)
<3.000 pg/ml	2	10%	17	89.5%		
>3.000 pg/ml	18	90%	2	51.3%		
Number of Oocyte						
< 12	6	31.6%	19	100%	81	(4.2-1561.6)
> 12	13	68.4%	0	0%		

OR : Odds Ratio; E2: Estradiol; AFC : Antral Follicle Count.

Discussion

According to an article by Pfeifer et al, [7] fair evidence was described concerning several patients' characteristics which were associated with an increased risk of OHSS. But there were still cut points that require validation; respectively the AMH values >3.4 ng/ml, development of ≥ 25 follicles, estradiol levels > 3500 pg/ml, and ≥ 24 oocytes. This article also mentioned contradictory reports on the predictive ability of a lower BMI to be associated with OHSS. Studies focused on the demographics of women who experienced OHSS may prove as an important tool to identify high-risk patients. Although several reports have been conducted in Asian countries, [8–10] studies in Indonesia are still very much needed. Considering risk factors of OHSS may differ in Asian women, due to environmental factors, genetics, and drug-use behaviors. [9]

Most of the women in the OHSS group experienced mild symptoms of OHSS. Which is in accordance with a report which states mild OHSS is the most frequent complication of ART in Indonesia[11] Most of the women with OHSS had 5 – 10 antral follicles, which was similar to a study in Scandinavia by Kahnberg et al. [12] most of the subjects had an AFC of 5 – 10 follicles, 54% in women that were admitted for OHSS and 53% in the non-OHSS group. Our data reports a significant difference in the AFC of the two study groups. Women with higher AFC were more likely to have OHSS than women lower AFC. These results are also in agreement with a case-control study by Shields et al. [5] that shows a higher follicle count was associated with a significant relevance ratio (RR) for OHSS (RR 1.4,p< 0.001(95% CI 1.29-1.52)). Antral follicles are oocytes surrounded by granulosa cells. The growth of the antral follicles is indicated by an increased volume of the oocyte, granulosa cell proliferation, and expansion from the antral space. This process can take up to 6 months and is affected by local factors and FSH levels, and not affected by the hormonal cycle. This may suggest that a high AFC may indicate a shorter period of follicles maturation, and a higher response of the ovarium to the stimulation. [13]

Our data suggested that the increased concentration of estradiol over 3000 pg/ml on the day of hCG administration, increases the risk of OHSS. This is in line with the previous report by Tarlatzi et al., [14] that showed estradiol levels on the day of hCG were associated with an increased risk of OHSS, OR 1.8 (CI 95% 1.5–2.15) for moderate OHSS and OR 2.8 (CI 95% 1.8–4.37) for severe OHSS. However, a study conducted in Thailand suggested that estradiol alone cannot predict OHSS. [9] According to a review by Mascarenhas et al., [15] the role of high estradiol levels in the pathology of OHSS still remains inconclusive. This review discussed that high levels of estradiol is merely a causative factor in the pathogenesis of OHSS. It is hypothesized a high ovarian response causes the increase in estradiol levels and triggers other vasoactive mediators such as VEGF, which ultimately leads to an increase in vascular permeability. Another opinion is that high estradiol levels are considered to actually be capable of triggering inflammation and protein release from the vascular space, yet do not enhance the inflammation. In addition, according to Shields et al. [5] increased levels of estradiol are a predisposing factor for thromboembolism in women with OHSS. Although the exact pathology of OHSS is still not fully understood, the hCG is suggested to play a part in inducing VEGF release and together with cytokines causes clinical manifestations of OHSS. [16]

Most of the women in the OHSS group had an oocyte count of more than 12 oocytes. Comparing this result with the non-OHSS group, in which most had lower than 8 oocytes and none had oocyte count higher than 12 oocytes. Thus, our data also showed a significant difference in the oocyte count between the two groups. Several studies also demonstrated similar results to our findings. [12,14] Our data also revealed that an oocyte count of more than 12 oocytes increased the risk of OHSS. A similar result was reported by a study conducted by Lee et al. [8] which described the oocyte count with cut off value of ≥ 11 oocytes had a sensitivity of 90.5% and specificity 66% may lead to the diagnosis of OHSS. The number of oocytes is believed to be the most direct measurement of ovarian response. However, it is still important to consider other possible factors, which may affect the accuracy of the oocyte count. Oocyte aspiration may be affected by problems in the final stimulation and aspiration process.[13]

In both groups, subjects' age and BMI were not significantly different. These results were in agreement with previous reports, a study in China also did not describe a significant difference for age in the two groups (p = 0,871), with an average age of 32 ± 4 years in the OHSS group and 32 ± 3.8 years in the non-OHSS group. [10] As well as a study by Shields et al. [5] reports that a lower BMI was not associated with an increased risk of OHSS RR 1.1 p = 0.19 (CI 95% 0.96–1.26). Whereas contrarily to a study in the United States by Luke et al.

which reported a significant difference for age $p< 0.001$, with an average of 35.6 ±4.6 years in the control group and 33 ± 4.3 years in women with moderate OHSS. [17] The previous study was conducted with a much bigger study population of over 1777 fertility clinics and 214,213 ART cycles of a 3 year period. Results also differ from a prospective study in Bangkok by Aramwit et al.,[9] reported a significant difference in BMI between the two groups ($p < 0.01$). Their data showed the BMI in 14 women with OHSS was lower with an average of 17.5 ± 6.9 (15.8–22.6) kg/m2, in comparison to 115 women who did not experience OHSS had an average BMI of 23.3 ± 7.6 (16.9–30.5) kg/m^2. Subsequently, these data raised a question of why some women with high ovarian response develop OHSS, while others do not. An interesting study on soluble protein, which binds to VEGF may explain this phenomenon. For example, the soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) which acts as a regulator of bioactivity, binds to VEGF to inhibit VP21 and prevents OHSS. This was achieved due to the ability of sVEGFR-1 to compete with VEGFR2 that binds with VEGF. [4] This theory is supported by the findings of Gomez and colleagues, which reported that women, showing a normal or excessive response of the ovaries and did not develop OHSS, had high levels of plasma sVEGFR-1 antagonists. Whereas the group which experienced hyperstimulation had lower sVEGFR-1 and higher free/ bound VEGF levels. Furthermore, according to another study which evaluated the cut-off value of OHSS risk factors, the sensitivity of age and BMI were not as good as other characteristics. The cut-off for age was 33 years old (sensitivity 76.2% and specificity 56%) and BMI was 18.66 kg/m^2 (sensitivity 33.3% and specificity 90.3%). Other predictive variables with better sensitivity assessed in the previous study were; estradiol levels on hCG injection day, AMH levels, number of follicles ≥ 10 mm on hCG injection day, and the oocyte count.[8]

This study has several limitations. Our data indicate a high odds ratio value for estradiol levels and the number of oocytes. This may be explained by the small sample size. Moreover, this is a cross-sectional study and as such missing data on medical records commonly occur. Protocols of ovarian stimulation and preventive measures for OHSS were not assessed in this study.

To the best of our knowledge, this is the first study that analyzed the risk factor of OHSS in Indonesia. Considering the life-threatening consequences of OHSS and the increasing number of its occurrence in Indonesia it is important to advocate more reports on OHSS as well as its preventive strategies. The current study provides an insight into which factors can be accounted for as a measure of a high ovarian response. Therefore, clinicians and fertility clinics practicing IVF procedures can provide appropriate preventive measures to reduce the risk of OHSS.

Conclusion

Women, who underwent IVF and developed OHSS had a higher antral follicle count, higher estradiol levels, and higher number of oocytes in compaison to women who did not experience OHSS. Women with AFC above 10 follicles, estradiol levels above 3000 pg/ml, and oocytes count of more than 12 were more likely to develop OHSS. This study adds informative data, which should help clinicians practicing IVF to establish preventive measures and develop protocols in order to prevent OHSS in high-risk patients.

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