Hematocrit as a simple method to predict and manage ovarian hyperstimulation syndrome in assisted reproduction

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Received: 05.02.2015
Review completed: 16.04.2015
Accepted: 04.05.2015

Access this article online
Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/0974-1208.158616

ABSTRACT

AIM: The aim was to analyze the hematocrit levels in cases of ovarian hyperstimulation syndrome (OHSS), syndrome occurring during *in-vitro* fertilization (IVF), and study its role as a prognostic indicator. **SUBJECTS AND METHODS:** Two years data of 66 women at high risk for developing OHSS was analyzed. Twenty-seven women who developed OHSS were further analyzed based on their hematocrit levels on the day of oocyte pick-up (OPU) and the day of embryo transfer (ET) to see if there was a prognostic trend. **RESULTS:** Of the total 225 IVF cases, 66 were deemed high risk for developing OHSS. Twenty-seven of these developed OHSS (40.9%). Of these 27, 21 (77.8%) had a hematocrit >35% on the day of OPU. The mean hematocrit in women developing OHSS on the day of OPU was 37.39% (standard deviation [SD] 2.66) as against 35.97% (2.80) in those not developing OHSS. This difference was statistically significant ($P = 0.043$). On the day of ET, 23/27 (85.8%) who developed OHSS had a hematocrit of >35%. The mean hematocrit was 39.29% (SD 3.85) in those who developed OHSS as against 34.7% (2.88) in those who did not. This difference (4.85) was statistically significant ($P < 0.001$). **CONCLUSIONS:** Women undergoing IVF were at a higher risk of developing OHSS when their hematocrit on the day of OPU and ET was >35%. Those who required cancellation of ET had a hematocrit of >35% on the day of ET or showed a significant increase of 3% from OPU to ET.

KEY WORDS: *In-vitro* fertilization, ovarian hyperstimulation, hematocrit

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is one of the main iatrogenic complications of controlled ovarian hyperstimulation in assisted reproduction.[1] It occurs after triggering ovulation with exogenous human chorionic gonadotropin (hCG) and may be aggravated by pregnancy.[2] The incidence of moderate OHSS with assisted reproductive techniques (ART) is 0.1–3.0%.[3] OHSS can have potentially fatal consequences in 3/100,000 stimulated women.[4]

Some of the factors that increase the risk of developing OHSS are younger age, low BMI, previous history of OHSS, history of exaggerated response to gonadotropins in intrauterine insemination cycles and presence of polycystic ovarian syndrome (PCOS).[5] Certain parameters have been studied and are said to be helpful in predicting the development of OHSS. These are a high estradiol level, high leucocyte count, higher follicular size and number, and elevated inhibin B levels.[6] None of these parameters have been proved to be independently predictive of OHSS.[3]

In women prone for OHSS, when hCG is given for ovulation, ovaries get hyperstimulated. There is an increase in various interleukins, causing increased capillary permeability resulting in fluid shift from intravascular to the extravascular compartment. This leads to ascites, occasionally pleural effusion and enlarged ovaries.[7] The rapid fluid shift also causes hypovolemia and hemoconcentration. The hemoconcentration that occurs is reflected in the rise of hematocrit level.

This study was designed with the intention of assessing the role of hematocrit as the main prognostic predictor of OHSS.

Aim

To analyze the hematocrit levels in cases of OHSS occurring during *in-vitro* fertilization (IVF) and study its role as a prognostic indicator.

SUBJECTS AND METHODS

This was a retrospective, single center observational cohort study conducted at the Division of Reproductive Medicine, at a Tertiary Care Teaching Hospital. Data of patients undergoing IVF from January 2012 to January 2014 was included. Ethical approval was obtained from the Institutional Ethical Committee.

The records of all those who underwent IVF in this period were analyzed. These women underwent stimulation with an antagonist or long protocol. Ovulation trigger was given in the form of hCG 13,000 IU (Ovitrelle 250 mcg, 2 ampoules, by Merck Serono Europe Limited) when majority of the follicles reached a size of ≥ 18mm.[8] Estradiol level, total leucocyte count, and hematocrit levels were done on the day of oocyte pick-up (OPU). Following OPU, all those who had ≥ 10 oocytes retrieved and had an estradiol level of more than 1500 pg/ml became the target population for this study (n = 66).

A data chart recorded the following information: Stimulation protocol (agonist/antagonist), presence of PCOS; estradiol, total leucocyte count, and hematocrit level on the day of OPU and on the day of embryo transfer (ET); the number of follicles tapped at OPU and the development of OHSS.

Patients were observed for the development of symptoms and signs of OHSS.

The development of OHSS on the day of ET was classified according to the criteria suggested by Golan and Weissman.[9]

Mild OHSS: Nausea, vomiting, ovarian size <5 cm.

Moderate OHSS: Abdominal distension, ascites along with nausea, and vomiting with ovarian size more than 5 cm.

Severe OHSS: Massive ascites, hemoconcentration (>45%) (the hemoconcentration criterion was not utilized in our classification, as this was the parameter under study), breathlessness, oliguria, enlarged ovaries.

If the OHSS symptoms on the day of ET appeared severe, a decision was taken regarding deferring ET and treating with albumin/cabergoline.

Based on the hematocrit results, the subjects were divided into three groups for analysis:

- Group 1: 30.0–34.9%
- Group 2: 35.0–39.9%
- Group 3: ≥40.0%.

Statistical Package for Social Science (SPSS) version 15.0 was used for statistical analysis. Categorical data were expressed as numbers and percentages and numerical data as mean ± standard deviation (SD). Student's t-test and Chi-square test for proportions were used where appropriate. Statistical significance was defined as $P < 0.05$.

RESULTS

There were a total of 225 cases of IVF in the study period that underwent stimulation with antagonist or agonist protocol. Sixty-six of these became the target population for our study as described above who were deemed high risk for developing OHSS. Twenty-seven out of the 225 (40.9%) women developed OHSS. Not surprisingly, all the 27 women belonged to the 66 women who had been deemed high risk. Of the 66 women, 46 (70%) were stimulated with antagonist protocol while the remaining 20 (30%) with agonist protocol. In the 27 who developed OHSS, the antagonist protocol was used in 32.6% (n = 15) compared to the agonist protocol in 60% (n = 12). The mean age of the target population was 29.8 years (SD 3.55) and 45.5% (n = 30) of these had PCOS. The estradiol levels, total leucocyte count and hematocrit levels on the day of OPU, in the 66 women is illustrated in Table 1.

Of the 27 women who developed OHSS 13 (48.2%) developed mild OHSS, 7 (25.9%) had moderate, and 7 (25.9%) had severe OHSS as per the Golan classification mentioned above.

Based on their hematocrit values on the day of OPU, the 66 women were divided into 3 groups. Those who developed OHSS were compared with those who did not, as shown in Table 2.

Of the 27 women who developed OHSS, 21/27 (77.8%) had a hematocrit of more than 35% of which 15/27 (55.6%) had a hematocrit between 35.0% and 39.9% and 6/27 (22.2%) had a hematocrit of more than 40%. Using the unpaired t-test, the mean for patient developing OHSS on the day of OPU was 37.39% (SD 2.66) while those not developing OHSS had an average hematocrit of 35.97% (SD 2.80). The difference of 1.4% with 95% confidence interval (0.5, 2.8) was statistically significant (P = 0.043).

The correlation between hematocrit subgroups on the day of ET and the development of OHSS is shown in Table 3.

The hematocrit levels of the 27 women with OHSS were next analyzed on the day of the ET. A total of 23/27 (85.8%) developed OHSS when their hematocrit on the day of ET was more than 35% of which 13/27 (48.2%) women had a hematocrit between 35.0% and 39.9% and 10/27 (37%) had a hematocrit of more than 40%. The mean hematocrit of those who developed OHSS was 39.29% (SD 3.85) and in those who did not develop OHSS was 34.7% (SD 2.88). The mean difference of 4.85 with 95% confidence interval (2.9, 6.2) was found to be statistically significant using the independent *t*-test ($P < 0.001$). Analyzing the sensitivity and specificity, the hematocrit value of more than 35% on the day of ET had a sensitivity of 85.2% and specificity of 48.7% in predicting OHSS. The diagnostic accuracy of the hematocrit on the day of ET in predicting OHSS was 83.5% [Figure 1]. The negative predictive value was 81.8% while the positive predictive value was 52.3%.

With the increase of hematocrit to more than 35%, an increasing trend of OHSS was observed. The difference between median hematocrit on the day of ET and OPU was calculated and the difference of 3% was found to be statistically significant by Kruskal–Wallis test, χ^2 (3) =22.949, $P < 0.001$ [Figure 2].

Embryo transfer was cancelled in 9 cases (7 from the severe group and 2 from a moderate group of OHSS). Of these, 6 cases (66.6%) had a hematocrit of more than 35% on the day of ET. The remaining 3 had a hematocrit of <35%. Interestingly, however, there was a marked rise in the hematocrit (mean = 10%) from the day of OPU to ET in these 3 cancelled cases. Hence, the difference of hematocrit between the day of OPU and ET can also be a predictor of OHSS.

Table 1: Parameters on OPU day

	Mean (SD)	Range
Estradiol (pg/mL)	4725.39 (3149.39)	1585-20,350
Total leukocyte count (/μL)	10,316.6 (2281.4)	6300-15,800
Hematocrit (%)	36.55 (2.81)	30.00-43.00

OPU: Oocyte pick-up, SD: Standard deviation

Table 2: Correlation between OHSS and Haematocrit on OPU day

	Hematocrit on the day of OPU (*n* (%))		
	30.0-34.9	35.0-39.9	≥40.0
OHSS present (27)	6 (22.2)	15 (55.6)	6 (22.2)
OHSS absent (39)	13 (33.3)	22 (56.4)	4 (10.3)
Total (*n*=66)	19	37	10

OHSS: Ovarian hyperstimulation syndrome, OPU: Oocyte pick-up

Table 3: Correlation between OHSS and hematocrit on ET day

	Hematocrit on the day of ET (*n* (%))			
	<30.0	30.0-34.9	35.0-39.9	≥40.0
OHSS present (27)	0	4 (14.8)	13 (48.2)	10 (37.0)
OHSS absent (39)	2 (5.1)	16 (41.0)	20 (51.3)	1 (2.6)
Total (*n*=66)	2	20	33	11

ET: Embryo transfer, OHSS: Ovarian hyperstimulation syndrome

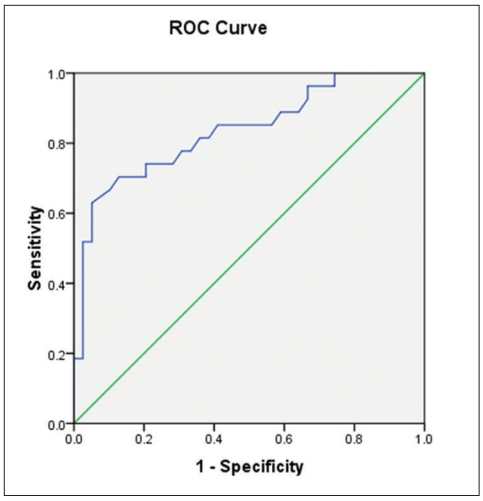

Figure 1: Receiver operating characteristic curve for the hematocrit on the day of embryo transfer

DISCUSSION

In this study, the incidence of OHSS was 12% with the incidence of severe OHSS being 2.7%. The incidence of severe OHSS varies between 0.1 and 3%.[3] According to a review of the epidemiology of OHSS, the incidence of OHSS was 8–23% which was consistent with the incidence in this study.[10] According to the Royal College of Obstetricians and Gynecologists, OHSS complicates almost 33% of cycles of ovarian stimulation and incidence of severe form varies between 3% and 8% of IVF cycles.[11]

Ovarian hyperstimulation syndrome adds to the emotional and financial burden of IVF and hence we felt a need to search for a simple marker which could help predict development of OHSS and manage the situation better, avoiding the associated morbidity.

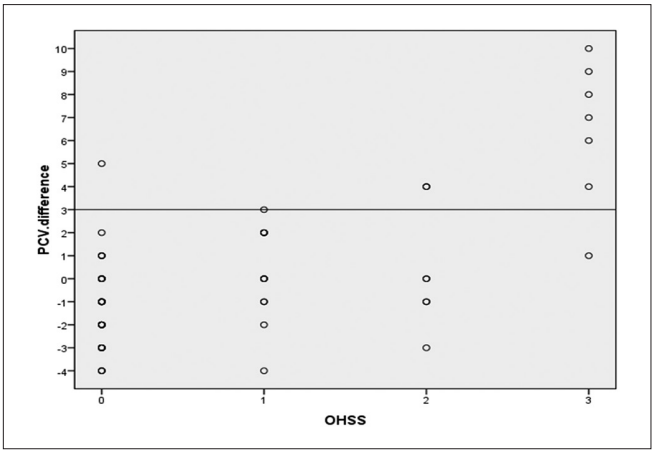

Figure 2: Scattergram

Risk factors suggested for OHSS are PCOS, age (<35 years), multifollicular response, high estradiol on the day of HCG and lean habitus.[12]

In this study, 45.5% (n = 30) subjects had PCOS as a risk factor. Of these, 53.3% (n = 16) developed OHSS. The value of PCOS in predicting OHSS was thus found to be limited (Pearson χ^2 (1) =3.512, P = 0.061).

High serum estradiol level was once considered to be a marker of OHSS. In this study, all the 66 subjects had an estradiol of 1500 pg/ml. Mean estradiol level was almost the same in patients who developed OHSS (Q_2=3935) and those who did not (Q_2=3853).This difference when calculated by Kruskal–Wallis test, χ^2 (3) =2.81, P = 0.422 (P > 0.05) showed to have a limited significance. This is similar to the findings of Papanikolaou *et al*. They reported that even at the best cut-off value in their study, high levels of estradiol as a risk factor is not very reliable in the prediction of OHSS.[13] This study had taken estradiol above 3000 pg/ml as high risk for OHSS. We have found that 22% of our OHSS cases (6/27) would have been missed if we had used the cutoff of 3000 pg/ml as a threshold to select our subjects at risk for OHSS. We instead enrolled all the subjects yielding ≥10 oocytes at OPU and estradiol ≥1500 pg/ml. This is in keeping with the recent evidence that high estradiol level is not necessary for the development of OHSS and in fact women with low estradiol due to desmolase gene mutation can develop OHSS.[14] Moreover, familial spontaneous OHSS has been reported by a few authors. The explanation in these patients is that mutations in the FSH receptors can cause inappropriate stimulation of these receptors by hCG causing spontaneous OHSS.[15]

We found that the hemoconcentration established by an increase of hematocrit of more than 35% on the day of OPU was more likely to result in OHSS (n = 21 [77.8%]). When the hematocrit on the day of OPU was more than 40% (n = 10) almost 60% of the subjects developed OHSS. When plotted on a receiver operator characteristic curve (area under the curve = 62.4%), the hematocrit on the day of OPU had a 77.8% sensitivity for predicting OHSS but a poor specificity (33.3%).

Sensitivity of the hematocrit level on the day of ET in predicting OHSS was 85.2%, with the diagnostic accuracy of 83.5%. Due to the low prevalence of OHSS, the positive predictive value was 52.3%. However, when the hematocrit on the day of ET was <35%, the chances of developing OHSS are small; with a negative predictive value of 81.8%.

Nine patients had symptoms and signs severe enough to have their ET deferred. Six of them (66.6%) had a hematocrit level of more than 35%. Three patients whose hematocrit was <35% on further evaluation were found to have an increase in hematocrit level from the day of OPU to that of ET. The hematocrit difference between the day of OPU and ET was found to be significant in predicting severe OHSS; χ^2 (3) =22.949, P < 0.001. The hematocrit difference of ≥3% was more likely to result in the incidence of severe OHSS.

Predicting the occurrence of OHSS, therefore, justifies the use of hematocrit as a simple test.

Another predictor of OHSS suggested by Verit *et al*. is the neutrophil: Lymphocyte ratio which was found superior to platelet: Lymphocyte ratio with a sensitivity of 85% and specificity of 78%.[16] The sensitivity of this test was comparable to our study. However, it can be argued that hematocrit is a much simpler and cheaper parameter to analyze compared to the above ratios.

Quantitative 3D Doppler angiography has also been studied as a predictor of OHSS. There was no demonstrable increased ovarian blood flow between the women who developed OHSS and those who did not, thus disproving the hypothesis.[17]

Serum inhibin B also had been reported to be useful in the prediction of OHSS. Chen *et al*. found that a day 5 inhibin B level as a good predictor for OHSS in the normal to high response group in comparison to the poor ovarian response group. This study had a sensitivity of 82.8% and a specificity of 99.1% when the inhibin B cut-off was 400 ng/l.[18] Inhibin B levels are not regularly estimated in our set up and hence could not studied. In fact, another study where follicular fluid and serum levels of inhibin A and B were used to predict OHSS, it was found that neither of them by themselves could predict OHSS. However, indices calculated using these levels appeared to be more promising.[19]

AMH is a more recent kid on the block. Apart from being considered a good predictor of the ovarian response to controlled ovarian hyperstimulation, its role in predicting OHSS is also encouraging. In the study by Lee *et al*., AMH was found to be a better predictor of OHSS than age and BMI as well as marginally better than the estradiol level on the day of HCG.[20]

This is the first study of using hematocrit levels as a predictor of OHSS in an Indian population. The limitation of this study is that it is a retrospective analysis and the sample size is small. Hence, larger prospective studies would be would be beneficial.

CONCLUSION

This study shows that hematocrit is a simple, inexpensive and fairly accurate test for predicting the development of

OHSS in ART. There should be a thorough assessment and a low threshold to defer ETs in women with a hematocrit of more than 35% on the day of ET or those showing an increase of ≥3% from the day of OPU to ET.

ACKNOWLEDGMENTS

The authors would like to thank Dr Asha Kamath for her help with statistics.

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How to cite this article: Kaur T, Pai P, Kumar P. Hematocrit as a simple method to predict and manage ovarian hyperstimulation syndrome in assisted reproduction. J Hum Reprod Sci 2015;8:93-7.
Source of Support: Nil, **Conflict of Interest:** None declared.