

The Role of Autonomic Neuropathy in Predicting Ovarian Hyperstimulation Syndrome

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Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is a life-threatening iatrogenic complication of ovarian stimulation during the assisted reproductive technique. **Objective:** This study was aimed to elucidate the effect of autonomic neuropathy on the occurrence of OHSS during assisted reproductive techniques. **Materials and Methods:** One hundred subfertile women underwent ovarian stimulation. The ovarian response was diagnosed by hormone concentrations and vaginal ultrasound. Autonomic function tests were done for all patients using Ewing's protocol. **Results:** Twenty-eight percent of subfertile women involved in this study had autonomic neuropathy. Out of 100 infertile women undergoing ovarian stimulation, only 5 (5%) had been developed OHSS, all of them had autonomic neuropathy ($P < 0.05$). The sensitivity and specificity of the autonomic neuropathy for the occurrence of OHSS was 100% and 58% which was insignificant ($P > 0.05$). The best cutoff score associated with OHSS was ≥ 1.5 which detected from receiver operating characteristic curve. The odds ratio for the absence of OHSS in patients without neuropathy was 9.891, which was significant as compared with the patients with neuropathy ($P < 0.05$). **Conclusion:** The study concludes that ovarian stimulation may cause autonomic function disturbance which can predict OHSS.

Keywords: Autonomic function tests, ovarian hyperstimulation syndrome, subfertile women

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation (mainly by gonadotropin therapy) used during assisted reproduction techniques. Approximately, 3%–6% of females undergoing ovarian stimulation may develop OHSS most of them have mild-to-moderately severe disease.^[1] It is reported that the incidence of severe OHSS after gonadotropin stimulation is 0.1%–2%.^[2]

The disease is characterized by variable manifestations which typically begin within the first 24 h after the administration of human chorionic gonadotropin (hCG) and then became more severe within the next 7–10 days. These manifestations include hemoconcentration, pleural hemorrhage, ascites, and oliguria.^[3]

Many risk factors are seen to increase the incidence of developing OHSS including younger age, the presence of polycystic ovary syndrome, an exaggerated response to gonadotropin stimulation, and the development of multiple follicles (>20) before induction of ovulation.^[4]

The autonomic nervous system can affect several body functions; thus, autonomic dysfunction may present with different clinical features and neurophysiologic changes.^[5] The autonomic nervous system has an important role in the control of the functions of the ovary.^[6]

Burden *et al.* demonstrated that the hilar perivascular plexus is a site where adrenergic nerves enter the ovary, then small branches from this plexus pass to the adjacent steroid-dependent interstitial gland cells.^[7]

Recently, Zangeneh *et al.* demonstrated that sympathetic efferent fibers have an important role in regulating the blood flow of ovaries (vasoconstrictor activity) and also causing inhibitory activity on ovarian estradiol secretion.^[8] Furthermore, these efferent sympathetic fibers are activated by noxious cutaneous stimulation.^[6]

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Since OHSS is potentially fatal complication, so identification of patients at risk of it is important, so that they will not be treated with high-FSH doses and long GnRH-agonist protocols. At the same time, looking for factors that predict OHSS early can help in the prevention of the disease.

The study objectives are to investigate the role of autonomic neuropathy in patients planned to have ovarian stimulation in predicting OHSS.

MATERIALS AND METHODS

The present investigation was designed as a cohort study. Written informed consent was obtained from each participant.

A total of 100 subfertile patients were included with age group from 19 to 43 years. The study is done at the period between February 2015 and July 2017. All patients undergo autonomic function tests at late follicular phase. All patients were downregulated according to the short protocol. Ovarian stimulation was performed with recombinant FSH or human menopausal gonadotropin.

The testing of autonomic functions was carried out in the morning, at a quiet room, and at the end of the follicular phase. Patients were advised to cease coffee consumption and eating for the last 2 h before the testing.

Cardiac autonomic neuropathy (CAN) was evaluated according to the Ewing's protocol which uses five standard cardiovascular reflexes. It comprises Valsalva maneuver, response to deep breathing, orthostatic testing, and isometric exercise.^[9]

The severity of CAN was determined by gathering the results of the cardiovascular reflex testing [Table 1]. The results of each testing were marked as 0, 0.5, or 1 if it yielded normal, borderline, or abnormal estimate, respectively. Accordingly, the lowest and highest autonomic neuropathy results were 0 and 5, respectively. Consequently, autonomic neuropathy (AN) was defined as the presence of at least two abnormal tests or an AN results of ≥ 2 .^[10]

Statistical analysis using mean with standard deviation of the variables between patients and control with receiver operating characteristic (ROC) curve for finding of cutoff value and sensitivity and specificity of the test was done also depending on Statistical Package for the Social Sciences (SPSS) software version 17, (IBM).

RESULTS

Twenty-eight percent subfertile women involved in this study had autonomic neuropathy.

Cardiac autonomic neuropathy and intracytoplasmic sperm injection complication (ovarian hyperstimulation syndrome)

Out of 100 infertile women undergoing intracytoplasmic sperm injection (ICSI), only 5 (5%) had been developed OHSS, all of them had autonomic neuropathy ($P < 0.05$), as shown in Figure 1.

Regarding OHSS and infertility causes, most of OHSS occur in female infertility group ($n = 4$) Figure 2.

The sensitivity and specificity of the CAN for the occurrence of complication (OHSS) was 100% and 58% which was insignificant ($P > 0.05$). The best cutoff score associated with OHSS was ≥ 1.5 which detected from ROC curve as shown in Figure 3 and Table 2.

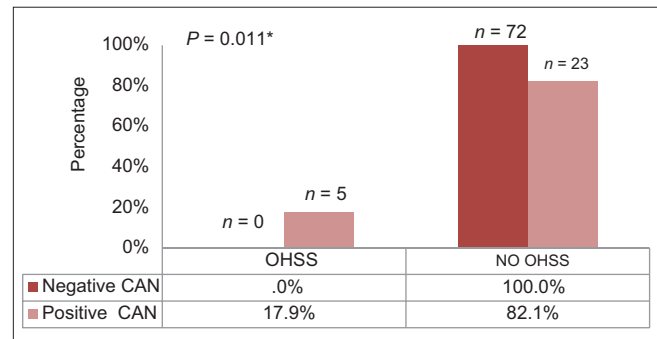


Figure 1: Autonomic neuropathy and the occurrence of ovarian hyperstimulation syndrome. CAN: Cardiac autonomic neuropathy, OHSS: Ovarian hyperstimulation syndrome

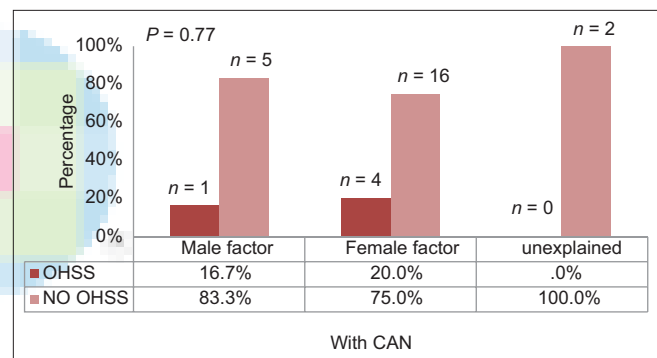


Figure 2: OHSS and subfertility causes. CAN: Cardiac autonomic neuropathy, OHSS: Ovarian hyperstimulation syndrome

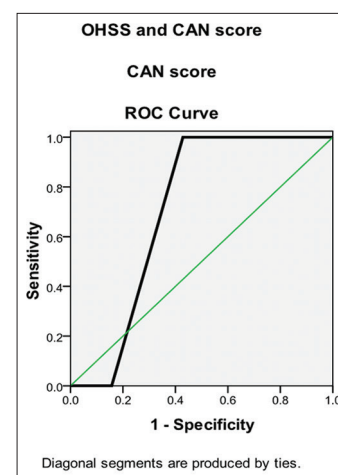


Figure 3: Receiver operating characteristic curve for OHSS and CAN score. CAN: Cardiac autonomic neuropathy, OHSS: Ovarian hyperstimulation syndrome

In binary logistic regression analysis, CAN shows statistically significant relationship with the existence of OHSS. The odds ratio (OR) for the presence of OHSS in patients with neuropathy was 5.625 (95% [confidence interval (CI)] 0.004–7066.341), as compared with the patients with no neuropathy [Table 3], and the OR for the absence of OHSS in patients without neuropathy was 9.891 (95% [CI] 1.038–94.229), which was significant as compared with the patients with neuropathy ($P < 0.05$).

DISCUSSION

It is well-known OHSS is a life-threatening iatrogenic disease, and so its prediction is a vital step in its prevention and treatment.

To the best of our knowledge, this is the first study analyzing the effect of preexisting autonomic neuropathy on the prediction of OHSS, and we found that at 1.5 neuropathy score the sensitivity for predicting OHSS was 100% and specificity 58%.

Accordingly, we recommend screening for women planned to have artificial ovarian induction, especially those at high risk for autonomic neuropathy like those with diabetes mellitus, repeated cycle of ovarian stimulation, smokers, or on drugs that impair the autonomic function (like α and β agonist or antagonist).

Table 1: Autonomic neuropathy score according to Ewing's protocol

AN score	Sum of points	AN
0	0	Absent
1	0.50-1.5	Early
2	2-3	Definite
3	≥ 3.5	Severe

AN: Autonomic neuropathy

Table 2: Sensitivity and specificity of autonomic neuropathy for the occurrence of ovarian hyperstimulation syndrome

Area	Cutoff point	Sensitivity (%)	Specificity (%)	P	95% CI	
					Lower bound	Upper bound
0.604	1.5	100	58	0.124	0.589	0.826

CI: Confidence interval

Table 3: Binary logistic regression analysis for ovarian hyperstimulation syndrome as the dependent variable

CAN	OHSS	P	OR	95% CI for odds ratio	
				Lower bound	Upper bound
With	With	0.635	5.625	0.004	7066.341
Without	Without	0.046*	9.891	1.038	94.229

*Significant. CI: Confidence interval, OR: Odds ratio, OHSS: Ovarian hyperstimulation syndrome, CAN: Cardiac autonomic neuropathy

The explanation for this finding is that since the exact pathophysiological mechanism of OHSS is not yet discovered and the most acceptable one is that OHSS results from increased vascular permeability in the region surrounding the ovaries. On the other hand, the autonomic nervous system has a profound role in maintaining the vascular integrity and homeostasis. Consequently, any impairment of autonomic nervous system is thought to have added detrimental effect on the vascular system and thus on developing OHSS.

Several researchers^[6-8] studied the effect of the autonomic nervous system on ovarian function, but this function is not yet fully clarified. As well as, no previous study investigated the role of autonomic neuropathy in predicting of OHSS during ovarian stimulation.

Many researchers found that OHSS is accompanied by elevation in the level of estradiol 2 and so they assume that estradiol 2 assay is an important marker to detect the majority of patients at risk of OHSS.^[11] On the same assumption, some investigators said that monitoring E_2 was found to be effective in reducing the incidence of OHSS.^[12] However, a level of E_2 threshold of 3000 pg/mL will predict only one-third of the total OHSS cases, while applying the best threshold value of 2560 pg/mL, less than half of the severe cases will be predicted (49% sensitivity and 77% specificity).^[11]

While Elprince *et al.* found that vascular endothelial growth factor and tissue factor can predict OHSS.^[4]

On the other hand, Griesinger demonstrated that the optimal threshold of follicles ≥ 11 -mm identify those at risk of OHSS was 19 follicles (sensitivity and specificity, 62.3% and 75.6%, respectively). The positive and negative predictive values were 6.9% and 98.6%, respectively.^[13]

In the present study, autonomic neuropathy scores were estimated according to Ewing's protocol.^[12] Based on the above facts, it is advised to monitor the level of estradiol E_2 and number of follicles on the day of hCG administration and delaying or cancelling it until the level of estradiol return to safe value (coasting protocol)^[12]

Zhao *et al.* demonstrated that microRNA (are a class of small noncoding RNAs that function as translational repressors) can be considered as biomarkers found in the blood for predicting OHSS in patients with polycystic ovarian syndrome.^[14]

The causes of autonomic neuropathy may be due to diabetes mellitus, nutritional factors (Vitamin B12 deficiency), hormonal factor, drugs used in controlled ovarian hyperstimulation, stress, genetic, or due to environmental factors.^[15]

Multiple therapeutic approaches are employed for the prevention of OHSS, including cycle cancellation, decreasing the dose gonadotropin (Gn),^[2] decreasing HCG dose or even induction of ovulation with GnRH – a trigger,^[16,17] cancellation of fresh embryo transfer, and also administration of hydroxyethyl starch or acetylsalicylic acid to prohibit aggravation of OHSS. Nonetheless, none of these approaches can eradicate the occurrence and progression of OHSS.^[18]

In vitro fertilization/ICSI stimulation protocol using HCG or LH usually induces maturation of multiple follicles in each ovary. This results in the release of vasoactive substances which act to increase vascular permeability, accumulation of fluid in third space, increase concentration of blood, and hypovolemia. All these events will induce OHSS.^[19]

CONCLUSION

Autonomic neuropathy is an important predictive factor of OHSS and should be kept in mind as risk factor for the disease.

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Conflicts of interest

There are no conflicts of interest.

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