ORIGINAL ARTICLE

Risk of gestational hypertension in pregnancies complicated with ovarian hyperstimulation syndrome

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Abstract

Objective: Ovarian hyperstimulation syndrome (OHSS) is the most common iatrogenic complication due to ovulation stimulation during assisted reproductive technology. Pathophysiology of this syndrome is not completely clarified, and there is no some specific treatment. Human chorionic gonadotropin is considered as the most significant factor in etiopathogenesis of OHSS. The results of some clinical studies related to influence of OHSS on pregnancy are variable. The aim of this study was to investigate hypertensive disease of pregnancies in patients admitted to hospital due to severe forms of OHSS with reference to maternal characteristics.

Methods: A case control study was conducted at the Obstetrics and Gynaecology Clinic "Narodni Front" and involved 50 patients admitted to hospital due to severe form of OHSS during a period from January 2008 to March 2015. A control group was created based on age and it involved 59 patients with pregnancy achieved with IVF/ICSI during the same period, but in which OHSS did not occur. For comparing mean values of continuous variables, Independent samples t test was applied.

Results: Patients with pregnancy complicated by OHSS, had considerably higher rate of hypertension (14% vs. 3.2 %, p=0.046)

Conclusions: Pregnancies achieved by IVF/ICSI, being complicated with severe OHSS could be related to gestational hypertension.

Keywords: IVF/ICSI, ovarian hyperstimulation syndrome, perinatal outcomes, hypertensive disease of pregnancy.

(JPMA 70: 1897; 2020) **DOI: https://doi.org/10.5455/JPMA.20387**

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most common iatrogenic complication due to ovulation stimulation during procedures included in assisted reproductive technology (ART). Incidence of a severe form of OHSS ranges from 0.5 to 5%.[1] Despite many years of clinical experience, there are no sufficiently reliable parameters based on which OHSS could be foreseen with certainty. Pathophysiology of this syndrome is not completely clarified, and there is no specific treatment. Human chorionic gonadotropin (hCG) is considered as the most significant factor in etiopathogenesis of OHSS.[2] Its presence results in oversecretion of mediators of granulosa and lutein cells, vascular endothelial growth factor (VEGF) is considered as the most responsible among these. Besides this, many cytokines have a significant role, particularly soluble receptor sFlt-1and interleukins. The basic mechanism for VEGF acting is increase of capillary permeability with collecting fluids within some third area and this most often leads to ascites or pleural effusion.[3] Fluid loss from the vascular space results in haemoconcentration, decreased renal perfusion with oliguria, and finally, acute renal insufficiency. In addition to this, haemaconcentration may lead to thrombosis. This sequence of events brings a patient into a life threatening condition. OHSS is categorized as early or late, depending on the time of occurrence. These two differ based on predisposing factors and their potential severity. Early OHSS is developed shortly after aspiration of oocytes and it reflects effects of exogenous hCG which is administered for final maturation of oocytes with previous stimulation with gonadotropins. Predisposing factors for its occurrence are younger age, polycystic ovarian syndrome (PCOS) and tubal or male sterility. Late OHSS occurs after 10 or more days after hCG administration and it is developed by endogenous production of hCG. It tends to be more severe than early OHSS and it is hard to be predicted.[4] The results of some clinical studies related to influence of OHSS on pregnancy are variable, and a number of such studies is relatively small. While some studies emphasized on increased risk of preterm labour and/or hypertension disorder in pregnancy, some of them implied frequent occurrence of gestational diabetes.[5-8] The aim of this study was to investigate hypertensive disease of pregnancies in patients admitted to hospital due to severe forms of OHSS with reference to maternal characteristics.

Methods

In the Obstetrics and Gynecology Clinic "Narodni Front", the case control study was conducted between January 2008 and March 2015. The study defines two groups of subjects, individual based, an experimental one which consist of 50

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patients, prevalence, (pregnancies complicated by ovarian hyperstimulation syndrome (OHSS) and a control consisting of 59 patients (pregnancies not complicated by ovarian hyperstimulation syndrome (OHSS). For comparing mean values of continuous variables, t-test of independent samples was applied. For applying two-sample significance test, where these two groups are equal (N1/N2=1), with a significance level α =0.05, strength of the study being minimum 0.8 (80%), and effect size of 0.6, the sample size calculated was at least 45 subjects per group. Fifty subjects per group were taken and the sample included total of 100 subjects. The calculation was done by the software G*Power 3,0,10. Inclusion criteria were patients in period between 2008 and 2015, all patients had a severe form of OHSS as per Navot and Golan's criteria,[8,9] all pregnant women gave birth at Obstetrics and Gynecology Clinic "Narodni Front". Exclusion criteria were patients with less than 4 obtained oocytes after aspiration, i.e. poor responders, patients with spontaneous abortion occurred in the first or second trimester and patients in whom OHSS developed, but who achieved pregnancy with IUI (intrauterine insemination).

The study was approved by the Institutional Research Ethics Board (record number 24/13-3). The study was conducted in accordance with the Helsinki Declaration and other nationally valid regulations. A control group was created based on age of patients in the study group. All patients involved in the study were nulliparous. The severe form of OHSS was defined based on criteria set by Golan et al. and Navot et al.[8,9] These criteria for a severe form of OHSS imply abdominal pain, ovary >5 cm and ascites (diagnosed with ultrasonography) or hydrothorax. In addition to aforementioned criteria for diagnosis of a severe form of OHSS, some of the following criteria were also required: haematocrit ≥45%, leukocytosis >15000/ml, oliguria <500ml/24h, increased levels of liver enzymes (values above the reference values for the laboratory), dyspnoea, anasarca or acute renal insufficiency.[8,9] Treatment for OHSS includes: bed rest, administration of crystalloid and colloid solutions, anticoagulation treatment as per indication, ascites drainage in case of dyspnoea or oliguria. The analyzed data in both groups included some characteristics of the patients and some perinatal outcomes. The studied characteristic in patients were age, infertility cause (PCOS, anovulation occurred due to some cause other than PCOS, tubal factor, endometriosis, male factor and idiopathic cause), BMI, total dose of gonadotropin, protocol, E2 values taken on a day when hCG was administered and a number of aspirated oocytes. PCOS has been defined as per Rotterdam consensus and which include two of three criteria: oligo and/or anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovaries.[10] Patients with less than 4 obtained oocytes after aspiration, i.e. poor responders were excluded from the study. In the time period of this study, there was no possibility for embryo cryopreservation at our Clinic. The studied perinatal variables included hypertension disorder during pregnancy (gestational hypertension and preeclampsia), intrauterine growth restriction (IUGR), and placental abruption. Hypertension in pregnancy was defined by blood pressure values being ≥ 140/90 mmHg taken after gestation week 20 while preeclampsia also included proteinuria being ≥300mg/24h.[11] The estimated body weight being under 10th centile was taken as a criterion for defining a foetus with IUGR. As already known, this group included numerous constitutionally small foetuses and therefore both dynamic of foeta growth and Doppler parameters were observed.[12] Placental abruption is defined as early separation of normally formed placenta before childbirth, but after gestation week 20 when diagnosis for placental abruption was made primarily based on clinical criteria (bleeding, abdominal pain and uterine hypertonus). Verification of retroplacental haematoma by an ultrasonography was evident in some cases, but it is not a mandatory diagnostic criterion.[13]

Results

The study included 50 patients admitted to hospital during early pregnancy due to severe form of OHSS. Of total 50 patients, 31 (62%) patients were with singleton pregnancy and 19 (38%), were with twin pregnancy. All pregnancies were achieved by IVF/ICSI. Early OHSS developed in 10 (20%) patients, while late OHSS developed in 40 (80%) patients. Paracentesis was executed in 12 (24%) patients . There was no statistical significant difference between the singleton and twin pregnancies regarding early and late OHSS and paracentesis as shown in Table-1.

Perinatal outcomes of pregnancies are presented in Table 2. Hypertensive disease occurred more in the study group (14.0%) than in the control group (3.2%); p=0.044). There is no statistical significance between OHSS and the

Table-1: Early and late OHSS and paracentesis between study and control groups (n (%)).

Variable	Answer	Pregnancy		Chi-square	Df	*p*-value
		Singleton	Twin			
Early OHSS	Present	7 (14)	3 (6)	0.177	1	0.674
	Not present	24 (48)	16 (32)			
Late OHSS	Present	24 (48)	16 (32)	0.177	1	0.674
	Not present	7 (14)	3 (6)			
Paracentesis	Present	10 (20)	2 (4)	1.810	1	0.178
	Not present	21 (42)	17 (34)			

There is no statistical significance between the singleton and twin pregnancies regarding early and late OHSS and paracentesis

Table-2: Diseases during pregnancy (n (%)).

	OHSS (n=50)	Control group (n=59)	*p*-value
Gestational hypertension	6 (12)	1 (1.6)	0.046
Preeclampsia	1 (2)	1 (1.6)	1.000
IUGR	6 (12)	2 (3.2)	0.139
Placental abruption	2 (3.7)	0 (0.0)	0.208

Gestational hypertension during pregnancy more often occurs in OHSS group than in the control group, p=0.046. When it comes to preeclampsia, IUGR and placental abruption there is no statistically significant dependence between the groups and these conditions, i.e. diseases;
IUGR-Intra Uterine Growth Retardation.

Table-3: Characteristics of the patients (mean value ± standard deviation or number (%))

	OHSS (n=50)	Control group (n=59)
Age (years)	32.47±3.92	33.60±3.54
BMI (kg/m^2)	22.47±314	21.92±2.44
Infertility cause		
PCOS	14 (28.0%)	11(18.6%)
Tubal	7 (14.0%)	4 (6.7%)
Endometriosis	5 (10.0%)	6(10.1%)
Anovulation	1 (2.0%)	0 (0.0%)
Male	8 (16.0%)	19 (32.2%)
Unexplained	15 (30.0%)	19 (32.2%)
Number of obtained oocytes	11.93±3.48	8.17±2.453
E2 values on a day for HCG (pg/ml)	2678.82 ±719.70	1702.90±700
Total gonadotropin dose	1759.78±395.09	2325.13±767.87

Statistically significant difference between the two categories occurs in a number of obtained oocytes (p<0.001), E2 values (p<0.001) as well as in total gonadotropin dose (p<0.001);
PCOS-Polycystic Ovary Syndrome.

control group regarding placental abruption (3.% vs 0.0%, p=0.208) and IUGR (12% vs 3.%, p=0.139) (Table-2).

The studied characteristics (demographic and clinical variables) are presented in Table-3. Significant difference between the study and control group was observed in the number of obtained oocytes (11.93 vs 8.17; p=0.000), E2 values (2678.82 pg/ml vs 1702.90 pg/ml; p=0.000), total gonadotropin doses (1759.78 vs 2325; p=0.000), as well as in a type of protocol (p=0.014) while BMI (22.47 vs 21.92) as a cause of infertility are similar in both groups: PCOS (28.0% vs 18.6%); tubal (14.0% vs 6.7%); endometriosis (10.0% vs 10.1%); anovulation (2.0% vs 0%); male (16.0% vs 32.2%); unexplained (30.0% vs 32.2%).

Discussion

Influence of OHSS on the course of pregnancy is still a subject of discussions, with a relatively small number of case control studies as per our knowledge.[14-16] Numerous factors such as multiple pregnancy rate, assessment of OHSS severity, patients' characteristics, infertility cause and ART, make interpretation of results rather complex. Considering demographic and clinical characteristics of patients with severe form of OHSS, significant difference occured for E2 values on the day when β-hCG was administered, the number of aspirated oocytes and gonadotropin dose. E2 values were significantly higher in OHSS group, as well as the number of aspirated oocytes while doses of administered gonadotropins were less. Higher values of E2 with lower gonadotropin doses could be explained by patients' predisposition for development of OHSS. In our study, a level of E2 was proved as a good prediction factor regarding development of OHSS. Chen et al. also implied this relation, while in studies conducted by Wiser et al. and Courbiere et al. E2 levels were relatively low and did not differ in comparison to the control group.[6,14,17] In addition to this, in our study, the study group had significantly higher number of oocytes, and this number was also proved to be a good prediction factor for development of early OHSS in other studies.[17] Protocol with antagonists was significantly more often used in the control group, while a long protocol with agonists was used in OHSS group. Such results could be interpreted with influence of antagonists as a possible prevention factor for development of OHSS. Numerous studies have shown that predisposing factors for OHSS are low BMI and younger age.[8] However, some authors have not found any significant difference in BMI among the studied groups and this is our case as well.[1] The control group of this case control study was created based on age of patients in the study group which explains why there is no significant difference in age between the groups.

Gestational hypertension significantly occurred more often in patients with OHSS in comparison to the control group, while rates of preeclampsia placental abruption and IUGR were not significantly different. The results of other authors are controversial. The most emphasized are increased risks for preterm labour and/or hypertension during pregnancy, while in some studies these include gestational diabetes as well.[7,16,18] Two previous studies suggested an increased risk for hypertension during pregnancy, as well as increased risk for preterm labour in patients with a severe form of OHSS.[6,19] Wiser et al. however, have not found any significant difference in hypertension rate during pregnancy whether these were singleton or twin pregnancies; although the incidence for hypertension was high in both groups (OHSS group and a group where pregnancy was achieved by IVF but in which a severe form of OHSS did not occur). Hypertension in pregnancy was diagnosed in 6.9% of singleton and 10.9% of twin pregnancies in OHSS group, while in the control group this was 8.2% and 7.0%, respectively. Hypertension rate in pregnancy among the general population ranges between 5% and 7%. [1]

Severe OHSS is characterized with increased vascular permeability and haemoconcentration as its consequence,

haemodynamic instability, which all could have influenced on placentation process in early pregnancy. Therefore, vascular and haemodynamic changes related to this syndrome can lead to potentially inadequate placentation i.e. trophoblasts invasion, and as final outcomes, hypertension disease, lower body weight and similar. [15]

Conclusion

Pregnancies complicated with severe OHSS can be considered at more risk for gestational hypertension in comparison to other pregnancies achieved by IVF/ICSI. However, lack of larger prospective studies imposes need for further investigations in order to make final and more accurate conclusions whether OHSS as an independent factor is a cause of poorer perinatal outcomes or whether there are other pre-existing factors such as cause of infertility, ART procedures themselves or possibly joined diseases.

Disclaimer: The manuscript is the part of PhD thesis.

Conflict of Interest: None.

Funding Sources: None.

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