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Ovarian hyperstimulation syndrome with spontaneous bacterial peritonitis and thrombocytosis: A Case Report

Síndrome de hiperestimulación ovárica con peritonitis bacteriana espontánea y trombocitosis: reporte de un caso

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SUMMARY

Introduction: *To date, severe Ovarian Hyperstimulation Syndrome (OHSS) that can be associated with mortality only occurred in 0.1 % – 2 % of all OHSS cases. This paper reports one of those rare cases accompanied by spontaneous bacterial peritonitis and thrombocytosis.*
Case Presentation: *A 28-year-old female had OHSS as a complication of in-vitro fertilization. Clinical presentation fever, dyspnea, ascites, thrombocytosis, leukocytosis, and bilateral multiloculated cystic ovaries. Fluid analysis revealed polymorphonuclears 545 cells/mm³. Treatment includes antibiotics, human albumin serum, low molecular weight heparin, and abdominal paracentesis. The patient was discharged after one week of admission and there were no recurrent OHSS events thereafter.*
Conclusion: *In patients with severe OHSS, urgent treatment with multidisciplinary management is mandatorily needed. If left untreated, OHSS can result in serious complications and even death.*

Keywords: *Ovarian hyperstimulation syndrome, spontaneous bacterial peritonitis, thrombocytosis.*

RESUMEN

Introducción: *Hasta la fecha, el Síndrome de Hiperestimulación Ovárica (SHEO) severo que puede asociarse con mortalidad solo ocurrió en 0,1 % - 2 % de todos los casos de SHEO. Este artículo reporta uno de esos raros casos acompañados de peritonitis bacteriana espontánea y trombocitosis.*
Presentación del caso: *Una mujer de 28 años tuvo SHEO como complicación de la fertilización in vitro. Presentación clínica fiebre, disnea, ascitis, trombocitosis, leucocitosis y ovarios quísticos multiloculados bilaterales. El análisis de fluidos reveló polimorfonucleares 545 células/mm³. El tratamiento*

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incluye antibióticos, suero de albúmina humana, heparina de bajo peso molecular y paracentesis abdominal. El paciente fue dado de alta después de una semana de ingreso y no hubo eventos recurrentes de OHSS a partir de entonces.

Conclusión: *En pacientes con SHEO severo, es obligatorio el tratamiento urgente con manejo multidisciplinario. Si es tratada, el SHEO puede provocar complicaciones graves e incluso la muerte.*

Palabras clave: *Síndrome de hiperestimulación ovárica, peritonitis bacteriana espontánea, trombocitosis.*

INTRODUCTION

Ovarian hyperstimulated syndrome (OHSS) is an iatrogenic complication that, in some cases, can be a potentially fatal physiological complication caused by ovulation induction during *in vitro* fertilization (IVF) cycles. The hallmark of OHSS is characterized by a fluid shift from the intravascular to the third space due to increased capillary permeability, ovarian neoangiogenesis, and cystic enlargement of the ovaries (1,2). The syndrome appears several days after starting gonadotropin induction therapy. Capillary permeability to plasma proteins increases, resulting in a fluid shift from the intravascular to the extravascular compartment, which clinically manifests as ascites, pleural effusion, oliguria, hemoconcentration, and electrolyte imbalances. The prevalence of mild OHSS is 20 %-23 % of IVF cycles, medium OHSS prevalence is approximately 3 %-6 %, and rare cases of severe OHSS about 0.1 %-2 %, have been reported (3).

Serious infection can appear in patients with OHSS when predisposing factors such as plasma immunoglobulin are lower than the normal value (4). Increased capillary membrane permeability and acute third-space fluid loss derived from excessive production of ovarian hormones and vasoactive substances result in the consequence of decreased intravascular volume and hemoconcentration which can lead to thromboembolism and death (5). This paper describes a woman with OHSS who developed an unusual complication, a serious infection: spontaneous bacterial peritonitis (SBP) and thrombocytosis.

CASE PRESENTATION

A 28-year-old female was admitted to the hospital and complained of chest pain and palpitations. The patient was six weeks pregnant, nine weeks after IVF was performed at the secondary hospital in Surabaya, but ovarian stimulation and ovulation induction protocols from this hospital were unknown. One week before this admission, she was discharged from another hospital with the same symptoms, and had been diagnosed with moderate OHSS, suffered from ascites and pleural effusion, required hospitalization for abdominal and pleural paracentesis, and received human albumin serum two times. She had also noticed abdominal enlargement after four weeks of pregnancy.

She complained of stomach pain, fullness, nausea, vomiting, weakness, decreased urine output, fever, chills, and weight increase, 4 kg in the previous week. She also experienced diarrhea three times per day for five days, but two days before admission, it had completely stopped. She also noticed a marked reduction in urine production. She was awake and alert, with a blood pressure of 90/60 mmHg, palpitations, a heart rate of 110 beats per minute, a temperature of 38.8 °C, an increase in respiratory rate of 30 times per minute, and a decrease in oxygen saturation of 92 %. However, after receiving 3 L/min of nasal oxygen supplementation, her oxygen saturation increased. Physical examination revealed ascites and a swollen abdomen. Abdominal ultrasonographic examination at admission revealed bilateral multiloculated cystic ovaries with a diameter of the right ovary of 10.6 cm, an estimated volume of 82 cm^3 (Figure 1) and a diameter of the left ovary of 10 cm, an estimated volume of 78 cm^3 (Figure 2) and ascites as well. Right pleural effusions were observed on thoracic radiographs and ultrasound (Figures 3 and 4). There was hemoconcentration and a significant increase in leucocytes which is suspicion of infection. Thrombocytosis was present, and albumin serum was below the normal range. Alanine transaminase (ALT) levels were slightly increased but aspartate transaminase levels were normal. Procalcitonin (PCT) increased from the normal limit and the erythrocyte sedimentation rate increased. The results of the viral hepatitis serology were negative.

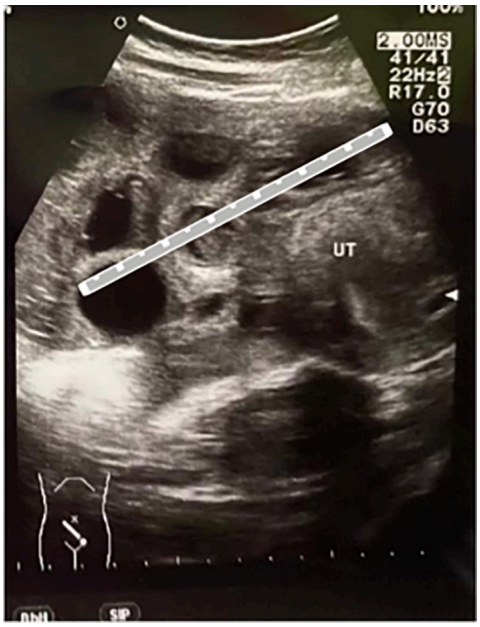

Figure 1. Right ovary diameter 10.6bcm, estimated volume 82 cm^3.

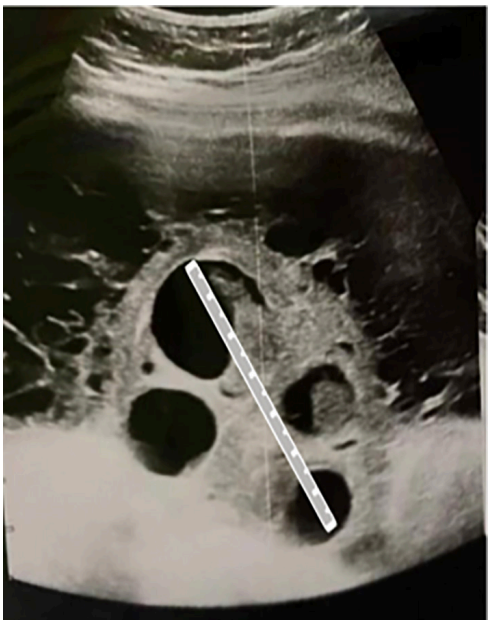

Figure 2. Left ovary 10 cm estimated volume 78 cm^3.

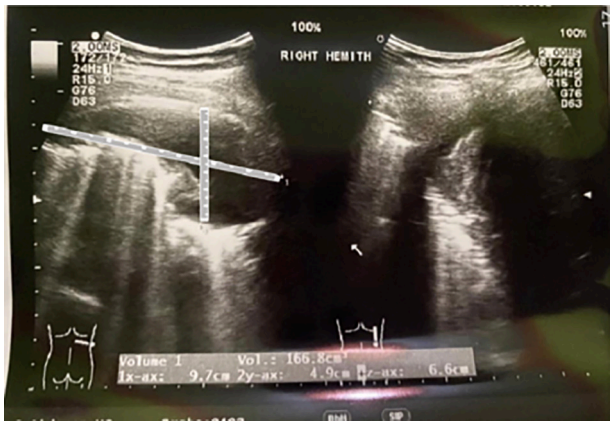

Figure 3. Right pleural effusion (9.7x6.6 cm), estimated volume 166.8 cm^3.

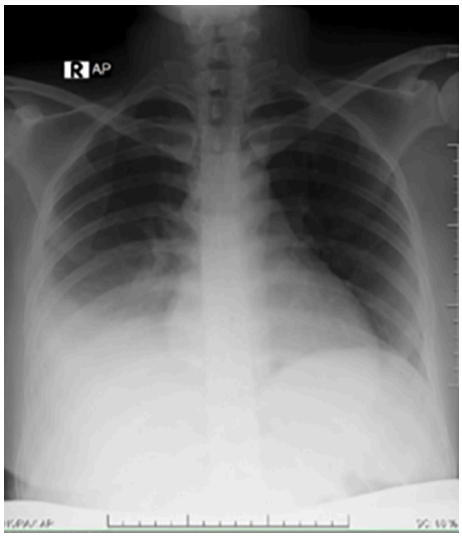

Figure 4. Right pleural effusion.

When OHSS was suspected, supportive care in the intensive care unit (ICU) was begun. At admission, 500 cm^3 of normal saline intravenous hydration and 25 % human albumin serum (100 mL/day) were started. The patient responded well, but his urine output was still insufficient. On the second day of admission, abdominal paracentesis with ultrasound guidance was performed, and 700 cm^3 of ascitic fluid were drained, followed by human albumin administration at a rate of 25 % 100 cm^3 per day. Ascites fluid analysis and culture were performed, as well as blood

culture. Cefotaxime was started at 2-g t.i.d. Fluid analysis revealed a significant increase in polymorphonuclears, indicating spontaneous bacterial peritonitis.

On the third day of admission, the patient was discharged to an internal ward after the hemoconcentration was resolved. For thromboembolic prophylaxis, low molecular weight heparin (fondaparinux sodium 2.5 mg once subcutaneously daily) was used. There were no thromboembolic events during treatment, oxygen saturation was normal after abdominal paracentesis, the patient no longer required oxygen supplementation, and the patient was able to perform her hospital activities independently. On the seven days of admission, blood culture and fluid ascites culture revealed no bacterial growth was found and platelets significantly decreased. Leucocytes also revealed normal, antibiotics were discontinued after seven days of treatment. The patient was discharged from the hospital after a total of seven days of hospitalization.

One week after being discharged from the hospital, the patient visited the outpatient department, in good condition, platelets decreased significantly, and the use of low molecular weight heparin was discontinued. On the second outpatient visit, she was in good health, her vital signs were normal, no ascites were found during the physical examination, and her platelets were normal (Summary laboratory tests performed upon admission were reported in Table S1 in the supplementary material).

DISCUSSION

The syndrome of ovarian hyperstimulation is an iatrogenic complication of supraphysiologic ovarian stimulation (6). The majority of OHSS is mild and causes little clinical concern in 20 % to 33 % of people. However, when OHSS is severe, it is occasionally associated with severe morbidity, and fatalities have been reported. Except in rare cases, OHSS occurs only after a luteinizing hormone surge or exposure to human chorionic gonadotropin (hCG). The reported incidence of moderate OHSS after gonadotropin superovulation for IVF is 3 % to 6 %, and for severe forms is 0.1 % to 2 %; the condition is potentially life-threaten. This case report defined SBP and thrombocytosis as complications of OHSS.

This case report presents a patient with a serious illness due to severe OHSS. OHSS was suspected when there was a recent history of ovarian stimulation followed by ovulation or hCG administration, according to The Society of Obstetricians and Gynecologists of Canada - Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee. An ultrasound will reveal large ovaries with multiple luteal cysts. Classic symptoms of moderate to severe OHSS include bloating, abdominal pain, rapid weight gain, and decreased urine output. The phenomenon is caused by the movement of intravascular fluid into the extravascular compartment, resulting in intravascular volume depletion and hemoconcentration, and thus hypercoagulability. This patient fulfilled all these clinical diagnoses.

The disease has been classified into various stages based on the seriousness of the condition according to the Golan (7) criteria and modifications by Navot et al. (8) in Humaidan et al. (9).

"Mild OHSS: grade 1 (abdominal distention and discomfort), grade 2 (grade 1 disease plus nausea, vomiting, and/or diarrhea plus ovarian enlargement from 5 to 12 cm).

Moderate OHSS: grade 3 (features of mild OHSS plus ultrasonographic evidence of ascites).

Severe OHSS: grade 4 (features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties), grade 5 (all the above plus a change in the blood volume, increased blood viscosity due to hemoglobin concentration, coagulation abnormalities, and diminished renal perfusion and function).

Chronic OHSS: grade 6 (ascites ± hydrotonic, Hct >55 %, white blood cell counts 25 × 10/l, oliguria, creatinine =1.6, creatinine clearance <50 ml/min, renal failure, thromboembolism, ARDS)".

The severity, in this case, included ascites, breathing difficulties, change in blood volume, increase blood viscosity due to hemoglobin concentration, leucocytosis (white blood cell

Supplementary material
Table S1 Summary Laboratory Test Performed Upon Admission

Item	Values	Normal Values
At the emergency room (First-day admission)		
Hemoglobin	15.1 g/dL	12.0-16.0 g/dL
Hematocrit	45.3 %	37-47 %
Leucocyte	36.6 103 /μL	4.0-10.6 103 /μL
Neutrophil	91.8 %	50-70 %
Platelets	721 103 /μL	150-400 10^3 /μL
Sodium	130 mmol/L	135-145 mmol/L
Potassium	4.0 mmol/L	3.5-5 mmol/L
Creatinine	0.6 mg/dL	0.51-0.9 mg/dL
Albumin serum	3.4 g/dL	3.5-5.2 g/dL
SGOT (AST)	20 U/L	<=31 U/L
SGPT (ALT)	47 U/L	<=31 U/L
Procalcitonin (PCT)	0.69 ng/mL	<0.05 ng/mL
Second days admission		
Hemoglobin	10.7 g/dL	12.0-16.0 g/dL
Hematocrit	34.1 %	37-47 %
Leucocyte	29.22 103 /μL	4.0-10.6 10^3 /μL
Neutrophil	90.2 %	50-70 %
Platelets	863 103 /μL	150-400 10^3 /μL
Ascitic Fluid analysis		
• yellowish color		
• clear		
• polymorphonuclears (PMN)	545 cell/mm^3	
• protein	3.2 g/dL	
• glucose	98 mg/dlL	
Five days admission		
Hemoglobin	9.6 g/dL	12.0-16.0 g/dL
Hematocrit	30.5 %	37-47 %
Leucocyte	13.98 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	89.7 %	50-70 %
Platelets	799 10^3 /μL	150-400 10^3 /μL
Seven days admission		
Hemoglobin	9.2 g/dL	12.0-16.0 g/dL
Hematocrit	29.0 %	37-47 %
Leucocyte	10.02 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	70.3 %	50-70 %
Platelets	664 10^3 /μL	150-400 10^3 /μL
Blood culture	No bacterial growth was found	
Ascitic fluid culture	No bacterial growth was found.	
Seven days after discharge (On outpatient department)		
Hemoglobin	10.2 g/dL	12.0-16.0 g/dL
Hematocrit	30.6 %	37-47 %
Leucocyte	10.01 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	70.2 %	50-70 %
Platelets	479 10^3 /μL	150-400 10^3 /μL
2 weeks after discharge (On outpatient department)		
Hemoglobin	11.2 g/dL	12.0-16.0 g/dL
Hematocrit	33.1 %	37-47 %
Leucocyte	9.8 10^3 /μL	4.0-10.6 10^3 /μL
Neutrophil	66 %	50-70 %
Platelets	357 10^3 /μL	150-400 10^3 /μL

count 36.600/μL), electrolyte imbalances (hyponatremia: sodium, 130 mmol/L), and elevated liver enzymes (10). OHSS is distinguished by increased capillary permeability, which results in ascites and effusion. Excess estrogens, progesterone, and cytokines are released because of hyperstimulation. This causes vascular endothelial growth factor secretion, which causes vascular hyperpermeability and a shift of fluids from the intravascular system to the abdominal and pleural cavities. As fluid accumulates in the third space, a patient may become hypovolemic and face circulatory problems (11). This is consistent with our patient's clinical presentation.

Fluid management is difficult in patients with severe OHSS due to the porous nature of the vascular bed. Women who can drink should, in general, be encouraged to drink to thirst rather than to excess. If the woman is unable to tolerate oral fluids, IV fluids such as normal saline should be started. Titrate the volume using the hematocrit as an indicator of hydration status. Excess intravenous fluids may aggravate the condition. The input/output balance must be constantly monitored (12). Diuretics should be avoided when there is hemoconcentration because they can cause critical OHSS. Diuretics should only be used when renal output is low despite normal hematocrit. Women with severe hemoconcentration (Hb >14 g/dL; Htc >45 %) need to be monitored (13).

In our case report, one of the complications of OHSS is evidence of SBP as a cause of sepsis, as determined by increased polymorphonuclears in fluid ascites analysis, which was successfully treated with antibiotics and intravenous human albumin administration. SBP is distinguished by the infection of ascitic fluid without an intraabdominal source of infection (11). The presence of more than 250 PMN cells/mm3 in the ascitic fluid indicates this condition and necessitates immediate treatment with antibiotics and human albumin serum. In 30 %-50 % of cases, ascitic fluid cultures are negative, and when positive, they typically grow gram-negative enteric bacteria (typically *Escherichia coli* and *Klebsiella pneumonia*). A lapse in antibiotic treatment could cause a significant and potentially fatal deterioration in clinical status. Infection can cause increased intestinal permeability, bacterial translocation into the bloodstream, changes in the systemic immune system, and impairment of ascitic fluid defense mechanisms. Patients with tense ascites that cause significant pain and/or respiratory compromise benefit from paracentesis. It can also improve oliguria caused by increasing intra-abdominal pressure and compromising blood flow to the kidney. The use of an indwelling pigtail catheter under ultrasound guidance eliminates the need for multiple drainage attempts and reduces the risk of infectious complications. The output of ascites should be recorded on daily basis. When paracentesis output begins to decrease as urine output increases, a clinical resolution occurs when the ascites output reaches 50 mL per day, the catheter can be removed. Ascites drainage will usually clear up a pleural effusion (13).

Thrombocytosis is an increase in platelets in the bloodstream. In severe cases, thrombocytosis can cause dangerous clots in blood vessels, thereby increasing the risk of a thromboembolic event. Secondary thrombocytosis is usually detected during routine laboratory testing, and most patients are asymptomatic. Patients may, however, experience symptoms related to the primary condition that causes thrombocytosis (14). Pregnancy is considered a hypercoagulable state due to the normal physiologic changes that affect coagulation. The pathophysiology of a thromboembolic event in OHSS is thought to be increased capillary permeability, resulting in hypovolemia and hemoconcentration, activation of the coagulation cascade, an increase in thrombin-antithrombin III, increased plasmin-antiplasmin complexes and increased platelets (12). Early detection and treatment are critical for both maternal and fetal health (15,16). The most serious life-threatening complication of OHSS is venous thrombosis. Preventive measures are recommended when there is a risk of thrombosis. Immobilization, pressure induced by large ovaries or ascites on pelvic vessels and hypercoagulable states due to pregnancy or high estrogen levels are all risk factors for thromboembolism in moderate-to-severe OHSS. Deep vein thrombosis is more common in patients who have a Leiden factor V mutation, antithrombin III deficiency, protein C

and S deficiency, and a personal or familial history of thrombosis (16,17). Using low-molecular-weight heparin improves the risk of thrombotic complications. Enoxaparin (40 mg/d) or dalteparin (5 000 IU/d) are recommended for thromboprophylaxis because they are easy to administer and do not require monitoring (17,18). Anticoagulation is advised for pregnant women and should be continued for at least the first trimester (19). There have been reports of late thrombosis up to 20 weeks after embryo transfer, and many researchers believe that heparin therapy should be continued for several weeks (20-22). Venous thromboembolism can occur even in mild OHSS, possibly due to the activation of the intrinsic coagulation cascade (23).

CONCLUSIONS

SBP, which results in sepsis, is a rare complication of OHSS. In OHSS, the combination of sepsis and capillary leakage causes hypovolemia and hemoconcentration, as well as activation of the coagulation cascade, which eventually leads to secondary thrombocytosis. To avoid further complications, such as thromboembolic events, immediate treatment with multidisciplinary management is required. When left untreated, OHSS can cause serious complications and even death.

Conflicting Interest(s)

The authors declare no conflict of interest.

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