A case report of spontaneous ovarian hyperstimulation syndrome and the long-term management of the endocrine disorder

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Background: Spontaneous ovarian hyperstimulation syndrome (sOHSS) is a rarely reported clinical symptom of uncertain origin with the incidence of 0.2–1.2%. There is no report of the patients' follow-up situation after the remission of the clinical symptom and this is the first one. The aim of this study was to remind the medical staff of the necessity of long-term management.

Case Description: We report a case of severe sOHSS with a normal 15 week gestation twin pregnancy in a 21-year-old primigravida who presented in our emergency room result from the 1 week's nausea and vomiting and progressively aggravated abdominal distension and pains for 3 days. The patient in our case had no significant precipitating factors and she had no previous outstanding medical history except that she had experienced acute glomerulonephritis when she was 9 years old. On ultrasound imaging, we found abnormally enlarged ovaries and massive ascites and moderate pleural fluid. A diagnosis of spontaneous ovarian hyperstimulation was made. The patient participated in followed-up visits for 1 year and experienced polycystic ovary syndrome (PCOS) and weight loss which up to 15kg after delivery.

Conclusions: Typically, although sOHSS is potentially life-threatening, its clinical detection is often delayed. A proactive strategy should be encouraged in the management of high-risk patients. The therapeutic schedule of mild-to-moderate sOHSS can focus on symptomatic relief and supportive treatment. Our case report elucidates the possible long-term effects of sOHSS and reminds us of the need for long-term management of those affected.

Keywords: Spontaneous ovarian hyperstimulation syndrome (sOHSS); twin pregnancy; long-term management; case report

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Introduction

Ovarian hyper-stimulation syndrome (OHSS) is commonly recognized as an iatrogenic complication of assisted reproductive technologies (ART). In rare cases, OHSS can also occur spontaneously in pregnant and non-pregnant women, who does not receive the ovary stimulation, that referred to as sOHSS, the incidence of which is reported as 0.2–1.2% (1). The pathogenesis of sOHSS is not understood clearly, it may result from the mutation of follicle stimulating hormone receptor (FSHR) or over secretion of glycoprotein hormones, such as β human chorionic gonadotropin (βHCG), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), and luteinizing hormone (LH) (2). The renin angiotensin system plays an important part in the pathophysiological process of sOHSS. Overstimulated ovaries release a variety of vasoactive mediators and some proinflammatory cytokines, leading to the increase of blood capillary permeability and activation of the renin angiotensin system (3), and finally cause the leakage of body fluid, hemoconcentration, oliguria, and electrolyte disturbance (4). According to existing research, sOHSS can happen to women who are pregnant, following

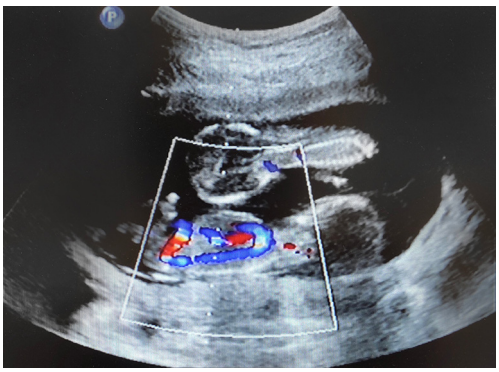

Figure 1 Abdominal ultrasonography of the fetus that revealed monochorionic diamniotic twins at 14 weeks of gestation. The red and blue part show the blood flow of the fetus.

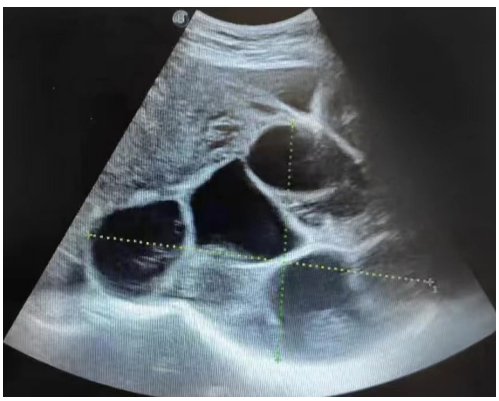

Figure 2 Abdominal ultrasonography of right ovary showed that the size of right ovary was 19.2 cm × 17.1 cm × 12.8 cm.

evacuation of a hydatidiform mole (5,6), and in women with thyroid (7,8) or pituitary disorders (9). This uncommon self-limited disease may be

familial and recurrent in selected patients (10). The precipitating factors and treatment are similar to those of OHSS. Women who are younger (<35 years), have a lower BMI, and a history of PCOS are at higher risk of developing sOHSS (11).

OHSS, including sOHSS, was classified into three categories with five grades according to Golan and Weissman (12). Grade 1 presents with abdominal distention, meanwhile, Grade 2 shows additional nausea, vomiting, and/or diarrhea and enlarged ovaries measuring 5–12 cm. These two grades belong to Mild OHSS. Moderate OHSS represents Grade 3 which not only presents with features of mild OHSS but also the ultrasound image of ascites. Severe OHSS shows Grade 4 with clinical evidence of ascites and/or hydrothorax and dyspnea and Grade 5 with change in blood volume, hemoconcentration, coagulation abnormalities, and the injury of kidney function.

However, the patient in our case was in the severe categories and had no significant precipitating factors and even more interesting is all the precipitating factors came out after the delivery. This study shows the long-term implication of sOHSS and reveals that the delivery may not be the end of sOHSS. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-827/rc).

Case presentation

A 21-year-old primigravida in low spirits, who had been experiencing nausea and vomiting for 1 week and progressively aggravated abdominal distension and pains for 3 days, presented in our emergency room with stable vital signs at 15 weeks gestation according to her last menstrual period. The patient was 163 cm tall and weighed 55 kg at admission. She had no previous outstanding medical history except that she had experienced acute glomerulonephritis when she was 9 years old. Prior to pregnancy, her menstrual cycle had been regular and she resolutely denied the history of ovarian stimulation or luteal support. The patient was admitted for blood test (serum gonadal hormone concentration, βHCG, thyroid function test, tumor marker, blood glucose examination, coagulative function evaluation, full blood count, renal and liver function test) and ultrasound. The blood parameters indicated hypoproteinemia and hypokalemia, and the rest were within their normal range. Transabdominal ultrasonography revealed monochorionic diamniotic twins of 14 weeks gestational age (*Figure 1*) and normal amniotic fluid. On ultrasound imaging, the ovaries stood out as severely enlarged and measured 19.2 cm × 17.1 cm × 12.8 cm and 23.2 cm × 15.8 cm × 9.4 cm on the right (*Figure 2*) and left (*Figure 3*), respectively. Multiple transonic cysts were observed, along with echogenic stroma giving a spoke wheel-appearance without solid component. There was massive ascites to a maximum depth of 7.2 cm and moderate pleural fluid (3.0 cm on left, 1.5 cm of right), but no pericardial fluid. A diagnosis of spontaneous ovarian hyperstimulation was made.

The patient was closely monitored according to her symptoms, urinary output, body weight, abdominal circumference, ultrasonography, and laboratory tests.

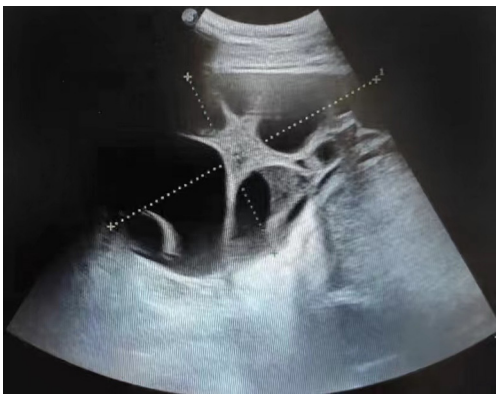

Figure 3 Abdominal ultrasonography of left ovary showed that the size of left ovary was 23.2 cm × 15.8 cm × 9.4 cm.

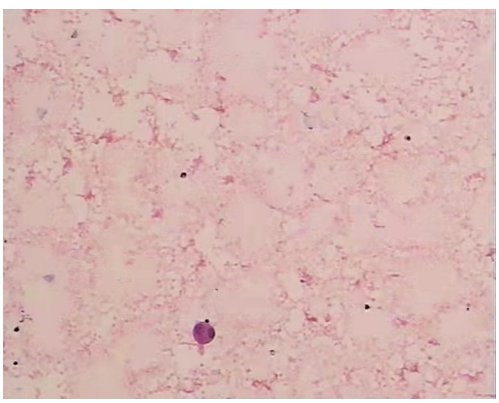

Figure 4 The cytological examination of the abdominal fluid which was observed by hematoxylin-eosin staining (×200) showing only mesothelial cells and inflammatory cells without malignant cells.

Continuous intravenous fluid (hydroxyethyl starch and human albumin solution) administration was implemented to correct her hemoconcentration. A prophylactic dose of enoxaparin was administered via hypodermic injection for venous thromboprophylaxis. We performed paracentesis a total of 5 times to discharge ascites on account of her unbearable abdominal distension, and 12,400 mL of hemorrhagic fluid was removed. The cytological examination of the abdominal fluid was negative for neoplastic cells (*Figure 4*). The patient was discharged on the 19th day of hospitalization. At hospital discharge, the ultrasound still showed bulky ovaries and moderate ascites of 4.2 cm, measured from the maximum depth. There were no signs of pleural fluid. The major axes of both ovaries were observed as having returned to 6.4 cm on obstetric imaging at 24 weeks' gestation, with no ascites noted. Meanwhile, she was diagnosed with hyperthyroidism at her prenatal visit. An emergency cesarean section was performed at 34 weeks' gestation due to twin-to-twin transfusion syndrome. The patient delivered 2 healthy male neonates.

The patient underwent follow-up visits for 1 year. Her thyroid function returned to normal levels involuntarily without pharmacological intervention after the delivery. Interestingly, the patient was diagnosed with PCOS on account of disordered menstruation which lasted up to 8 months postpartum. During the whole year following childbirth, the patient experienced steady weight loss, reaching 15 kg to date. Currently, she is undergoing long-term management of endocrine function via outpatient clinic. According to our case, the PCOS, thyroid dysfunction, and reduced BMI seems to be an outcome instead of predisposition. The development of disease and treatment time line during the hospitalization are summarized in *Table 1*. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Compared to OHSS, which is one of the most common complications in ART treatment cycles, sOHSS is characterized by no history of ovarian stimulation. It usually occurs at about 8–14 weeks of gestation (13) with low incidence. The pathogenesis of sOHSS is still unclear. On the basis of literature reports, 5 heterozygous activating types of FSHR mutation have been shown to be related to the development of sOHSS. Regarding the clinical features and presentation of the FSHR mutation, 3 different types of possible pathway were postulated (14). Type I is related to the recurrence of sOHSS which usually presents in patients with normal or low βHCG (12). This kind of mutation results in FSHR binding to not only FSH, but also the LH, HCG, and TSH which include similar beta subunits, that finally lead to hyper-sensitivity to HCG (15). The cascade of reaction mentioned above can trigger sOHSS. Type II is the most common type, generally presenting in diseases with high levels of βHCG, such as hydatidiform

Table 1 Summary of the treatment regimen and adverse event according to the patient.

Hospitalization day	Treatment regimen	Treatment line	Adverse event
2 to17	Hydroxyethyl starch and human albumin solution	1	Hemoconcentration
4	Prophylactic dose of enoxaparin	2	None
7	Paracentesis	3	Abdominal distension
8	Paracentesis	4	Abdominal distension
10	Paracentesis	5	Abdominal distension
12	Paracentesis	6	Abdominal distension
13	Paracentesis	7	Abdominal distension

mole and multiple gestations. High concentrations of serum βHCG increase the phosphorylation of vascular endothelial growth factor (VEGF) (16), and in this way, more fluid influx into the third spaces, which may compound the situation. In type III, there is hypothyroidism with high levels of TSH. The high-level TSH stimulates the ovaries which can impact the formation of follicles and secretion of estrogen via binding to FSHR (17). This can occur in the nulligravida and the condition improves with levothyroxine therapy (18). Similar to OHSS, sOHSS is self-limited. The therapeutic schedule of mild-to-moderate sOHSS can focus on symptomatic relief and supportive treatment. However, patients with severe sOHSS need to undergo necessary interventions including surgery. In contrast to OHSS, sOHSS is unpredictable. Therefore, close follow-up should be conducted for patients at high risk of developing severe sOHSS. Above all, final-period management should be taken seriously.

In our case, the patient had no history of previous endocrine abnormality before experiencing sOHSS. She was diagnosed with hyperthyroidism in her later-stage of pregnancy. After delivery, she sought medical advice for the oligomenorrhea and was diagnosed with PCOS, meanwhile, her thyroid function returned to normal without medical intervention.

Unfortunately, limited by the inspection technique, we did not do the further gene test in our case. We try to make the bold speculation that the hyper-sensitive to the hormone was retained even though the clinical symptom was disappeared and this kind of overreaction result in the endocrine disorders. As to this patient, she was treated with short-acting contraceptive "Yasmin" just as the same with patient with PCOS.

Our report aims at reminding clinician of taking the long-term management into account. As we know, patients with endocrine disorders always need long-term management to improve the quality of life. For sOHSS, even if we could not prevent the gene mutation, we should take long-term management that may reduce the risk of recurrence in her next gestation and improve the quality of life.

Conclusions

Compared with drug-induced OHSS, sOHSS is always detected comparatively late, due to the lack of supervision. Therefore, we should pay more attention to high-risk patients to avoid the risk of a life-threatening situation. When the progression is controlled, long-term management should be considered as far as possible.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-827/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-827/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Deligeoroglou E, Iavazzo C, Sofoudis C, et al. Management of hematocolpos in adolescents with transverse vaginal septum. Arch Gynecol Obstet 2012;285:1083-7.
2. Audebert A. Characteristics of adolescent endometriosis: apropos of a series of 40 cases. Gynecol Obstet Fertil 2000;28:450-4.
3. Sarıdoğan E. Adolescent endometriosis. Eur J Obstet Gynecol Reprod Biol 2017;209:46-9.
4. Brosens I, Gordts S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. Hum Reprod 2013;28:2026-31.
5. Arora R, Merhi ZO, Khulpateea N, et al. Ovarian hyperstimulation syndrome after a molar pregnancy evacuation. Fertil Steril 2008;90:1197.e5-7.
6. Strafford M, Moreno-Ruiz N, Stubblefield P. Ovarian hyperstimulation syndrome in a spontaneous pregnancy with a complete hydatidiform mole. Fertil Steril 2009;92:395.e1-3.
7. Taher BM, Ghariabeh RA, Jarrah NS, et al. Spontaneous ovarian hyperstimulation syndrome caused by hypothyroidism in an adult. Eur J Obstet Gynecol Reprod Biol 2004;112:107-9.
8. Edwards-Silva RN, Han CS, Hoang Y, et al. Spontaneous ovarian hyperstimulation in a naturally conceived pregnancy with uncontrolled hypothyroidism. Obstet Gynecol 2008;111:498-501.
9. Baba T, Endo T, Kitajima Y, et al. Spontaneous ovarian hyperstimulation syndrome and pituitary adenoma: incidental pregnancy triggers a catastrophic event. Fertil Steril 2009;92:390.e1-3.
10. Montanelli L, Delbaere A, Di Carlo C, et al. A mutation in the follicle-stimulating hormone receptor as a cause of familial spontaneous ovarian hyperstimulation syndrome. J Clin Endocrinol Metab 2004;89:1255-8.
11. Di Carlo C, Savoi
a F, Fabozzi A, et al. A case of ovarian torsion in a patient carrier of a FSH receptor gene mutation previously affected by spontaneous ovarian hyperstimulation syndrome. Gynecol Endocrinol 2015;31:105-8.
12. Golan A, Weissman A. Symposium. Update on prediction and management of OHSS. A modern classification of OHSS. Reprod Biomed Online 2009;19:28-32.
13. Rodien P, Beau I, Vasseur C. Ovarian hyperstimulation syndrome (OHSS) due to mutations in the follicle-stimulating hormone receptor. Ann Endocrinol (Paris) 2010;71:206-9.
14. De Leener A, Montanelli L, Van Durme J, et al. Presence and absence of follicle-stimulating hormone receptor mutations provide some insights into spontaneous ovarian hyperstimulation syndrome physiopathology. J Clin Endocrinol Metab 2006;91:555-62.
15. Mittal K, Koticha R, Dey AK, et al. Radiological illustration of spontaneous ovarian hyperstimulation syndrome. Pol J Radiol 2015;80:217-27.
16. Kim MK, Won HJ, Shim SH, et al. Spontaneous ovarian hyperstimulation syndrome following a thawed embryo transfer cycle. Clin Exp Reprod Med 2014;41:140-5.
17. Anasti JN, Flack MR, Froehlich J, et al. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab 1995;80:276-9.
18. Ilanchezhian S, Mohan SV, Ramachandran R, et al. Spontaneous ovarian hyperstimulation syndrome with primary hypothyroidism: Imaging a rare entity. Radiol Case Rep 2015;10:1050.

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