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Case Report

Right neck venous thrombosis following ovarian hyperstimulation syndrome in a patient with protein S deficiency: A case report and review of literature

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ABSTRACT

Objective: The risk of venous thromboembolism in pregnancies increased in ovarian hyperstimulation syndrome (OHSS) after assisted reproductive technologies (ART). We present a rare case with protein S deficiency receiving ART treatment with OHSS, following right neck venous thromboembolism.
Case report: A 34-year-old women with primary infertility underwent IVF treatment and presented with OHSS. However, thromboembolism in the right jugular and subclavian veins was diagnosed at eight weeks of gestation. She was continuously treated with low molecular weight heparin (LMWH) since eight weeks of gestation and the diagnosis of protein S deficiency was made. Due to placenta previa with massive bleeding, she gave live birth to two healthy babies via cesarean section at 34 weeks of gestation.
Conclusion: Thromboembolism is one of life-threatening complications among women with OHSS. Although inherited thrombophilia is rare diseases, thrombophilia workup may be taken into consideration for women with thrombotic events.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a complication of controlled ovarian hyperstimulation with exogenous gonadotrophin administration in assisted reproductive technologies (ART) [1]. Hemoconcentration and hypercoagulation status are associated with elevated serum estrogen. Although the thromboembolic complication after OHSS is rare, it may lead to critical neurological or cerebrovascular damage [2]. Thrombosis varies at clinical presentation, depending on the severity of the extent of thrombosis, from asymptomatic to life-threatening.

Protein S deficiency is a rare inherited thrombophilia that increases the risk of venous thromboembolism, especially during pregnancy [3]. Protein S is a glycoprotein dependent on vitamin K, and it acts as a non-enzymatic cofactor to activate protein C for inactivating procoagulant factors Va and VIIIa. Therefore, activated protein C and protein S reduce thrombin generation [4]. The incidence of protein S deficiency is still unknown in the general population, but the individuals with venous thromboembolism (free protein S < 33 units/dL) among this selected population is about 0.9% [5]. Because protein S deficiency is a rare inherited thrombophilia disease and only two previous cases had been reported, we demonstrate this case for further discussion.

Case presentation

A 34-year-old Taiwanese woman with body mass index 18.9 kg/m2 had primary infertility for 4 years due to right side tubal occlusion. Her medical history and operation history were unremarkable. Her serum anti-Mullerian hormone (AMH) was 2.08 ng/Ml, but the antrum follicle count of bilateral ovaries was 6. She received ART treatment of gonadotropin-releasing hormone (GnRH) antagonist protocol with recombinant follicle-stimulating hormone (FSH; GONAL-F®, Merck Serono, Aubonne, Germany) and GnRH antagonist (Orgalutran®, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany). By the 9th day of ovarian stimulation, there were seven follicles more than 16 mm and nine follicles less than 16 mm. Ovarian retrieval was performed 36 h after administration of human chorionic gonadotropin (hCG) (Ovidrel®, Merk Serono, Modugno, Italy) 6500 IU. Unexpectedly, the serum estradiol level on the day of hCG administration was 4460 pg/mL. A total of 16 oocytes were collected transvaginally. The best strategy for patients with risk of OHSS is the vitrification of all

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embryos or oocytes [6]. Before embryo transfer, we had informed the risky of OHSS and prolonged duration of the OHSS symptoms because of elevation of intrinsic hCG level [7]. However, she still decided to take risks and shorten the time to pregnancy interval for personal reasons. Finally, the decision-making is two blastocysts transferred to the uterus on day 5. Daily 90 mg of progesterone vaginal gel (Crinone® 8%; Serono Pharmaceuticals Ltd., UK) was started on the day after oocyte retrieval for luteal phase support.

One week after embryo transfer, she presented abdominal fullness, nausea, shortness of breath, weight gain of 5 kg, and decreased urine amount. Ultrasound revealed bilateral enlarged ovaries up to 6 cm in diameter with much ascites. Laboratory analysis reported no hemoconcentration. She was admitted for severe OHSS and treated with supportive care. The pregnancy test was positive and discharge was scheduled after improvement of symptoms. One week after discharge, transabdominal ultrasound revealed decreased ascites and two gestational sacs at five weeks of gestation.

At eight weeks of gestation, she presented with right swollen and painful neck, causing odynophagia. By physical examination, cellulitis or infectious diseases were less likely because local erythema and heat on the lesion site were not presented. The vital sign including body temperature, heart rate and respiratory rate were normal. The diagnosis of right jugular vein and subclavian vein thrombosis (Figs. 1 and 2) was confirmed by neck ultrasound. She refused the examination of computed tomography, so pulmonary embolism or other sites of embolism could not be confirmed. The D-dimer elevated to 3.12 ug/ml and fibrin degeneration product (FDP) also elevated to 11.9 ug/mL. She completed two-week course of thrombolytic treatment with enoxaparin 6000 IU every 12 h subcutaneously, following rapidly resolution of right swollen and painful neck. Because of this thromboembolism event, thrombophilia workup was carried out and the diagnosis of protein S deficiency (serum-free protein S was less than 10 percent) was made.

At 25 weeks of gestation, she was re-admitted for tocolysis due to massive vaginal bleeding and preterm uterine contraction. Transvaginal ultrasound indicated placenta previa of twin A. Enoxaparin was ceased at the time of hospitalization and resumed when vaginal bleeding stopped. However, she experienced uncontrollable preterm labor with massive vaginal bleeding at 34 weeks of gestation and underwent emergent cesarean section. The anticoagulant was stopped 24 h due to increased vaginal bleeding prior to operation. The birth weights of twins were 2060 gm and 2040 gm. The Apgar scores were both 9 at the first minute and both 10 at the fifth minute. Total intrapartum and postpartum blood loss was 1580 mL, suggesting postpartum hemorrhage. Poor uterine contraction was identified and she was managed with uterine massage, intravenous oxytocin drip and blood transfusion. She was discharged four days after cesarean section under stable condition. She continued anticoagulant treatment for postpartum 6 weeks.

Discussion

Thromboembolism event following OHSS or ART treatment was considered as one of the most serious complications in current evidence. Even without ART treatment, hypercoagulative status in pregnancy is currently known that several coagulation factors, such as factor I, II, VII, VIII, IX, and X increased while protein S decreased. From a review article in 2014 [8], among patients undergoing ovarian induction with ART treatment, thrombotic events in the veins (65%) were more than in the arteries (18%). The most common thrombotic veins were jugular vein and subclavian vein (71.8%), following lower extremities and cerebral vein. In patients with thromboembolic events, the cumulative percentage of thrombosis within 50 days after embryo transfer was 76 percent. Forty-five percent patients had underlying thrombophilia diseases. Another retrospective study reported most cases (49.5%) with the diagnosis of venous thromboembolism were prior to 15 weeks of gestation [9]. Compared with pregnancies without thrombophilia diseases, the pregnant women with inherited deficiency of antithrombin III, protein S, or protein C had an eight-fold increased risk of venous thrombosis during the period of pregnancy and postpartum [10]. The anatomic location of thrombosis and timing of occurrence in our reported case were compatible with recent published literatures.

Whether patients with inherited thrombophilia and OHSS had a much higher risk of thromboembolic events or not was controversial. To our knowledge, hypercoagulative status and hemoconcentration were the factors for thromboembolic events in patients with OHSS. The prevalence of thromboembolism in patients with severe OHSS was reported to be 0.78% [11]. Dulitzky M. et al. conducted a prospective study and the findings revealed higher prevalence of thrombophilia in women with severe OHSS. However, the prevalence of thrombophilia in women with mild or moderate OHSS remained unknown. Regarding the cost-effective issue, inherited thrombophilia disease is sporadic, and the cost

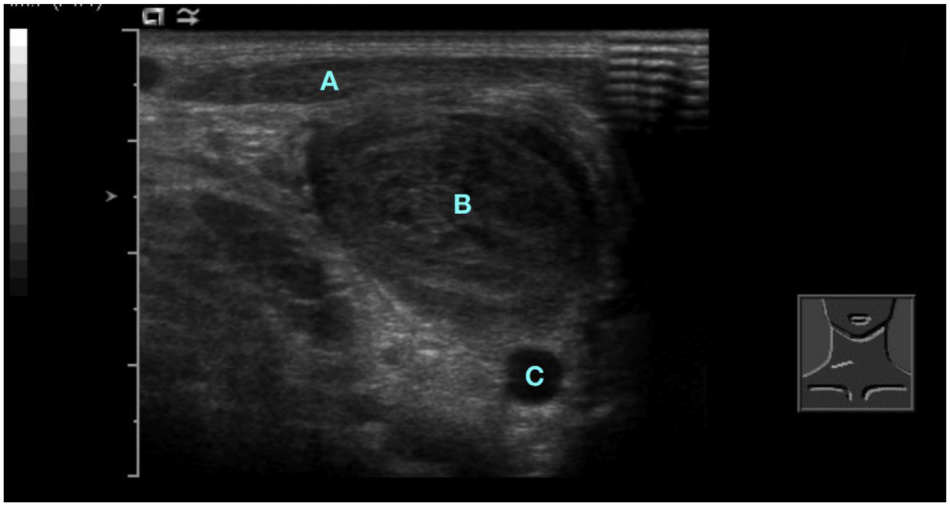

Fig. 1. Axial view of right neck; A: sternocleidomastoid muscle; B: thrombus in the internal jugular vein; C: common carotid artery.

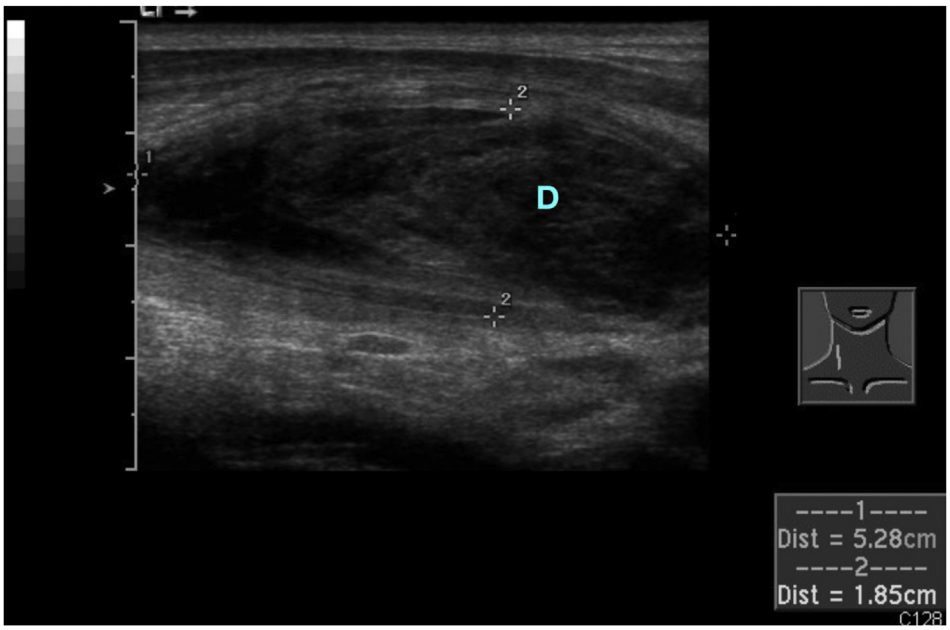

Fig. 2. Sagittal view of right internal jugular vein; D: thrombus in the right internal jugular vein.

Table 1
Summary of reported protein S deficiency cases with thromboembolic events following ovulation induction.

Author(s)	Arya et al. (2001) [16]	Thomas et al. (2001) [17]	Huang et al. (2020)
Maternal age	30	31	34
Ethnic origin	European	European	Asian
OHSS	no	no	yes
Pregnancy and outcomes	Yes, SAB at 18 weeks of gestation	Yes, SAB at 24 weeks of gestation	Yes, twin pregnancy with live birth at 34 weeks of gestation
Timing of thrombosis	8 weeks of gestation	2 weeks after ET	8 weeks of gestation
Thrombolic location	Right internal jugular and subclavian veins	Right internal jugular vein	Right internal jugular and subclavian veins
Treatment	IV UFH then LMWH	IV UFH then LMWH	LMWH

SAB: spontaneous abortion, ET: embryo transfer, IV UFH: intravenous unfractionated heparin, LMWH: low molecular weight heparin, OHSS: ovarian hyperstimulation syndrome.

effect of screening is prohibitive. Therefore, routine laboratory testing for the identification of heritable thrombophilia among all pregnant women is not cost-effective [12].

The value of serum estradiol could be evaluated to predict the possibility of OHSS. A case-control retrospective study summarized that the cut-off levels on the day of hCG administration was 3354 pg/mL to predict higher risk of OHSS (sensitivity and specificity were both 85%) [13]. Although cancellation of the cycle did not prevent the coming OHSS, this result could provide the “early sign” to prevent subsequent OHSS. We had informed this case of the risk of OHSS and prolonged duration of symptoms, so she immediately went back to our emergency department when onset of associated symptoms.

According to American College of Obstetricians and Gynecologists (ACOG) [14], the antepartum management for pregnant women with thrombophilia and previous one episode of thromboembolism is prophylactic LMWH or unfractionated heparin. The optimal timing of interrupting LMWH is as much as 24 h before surgery [15]. The risk of thromboembolism is also higher at the postpartum period and the anticoagulant treatment should be continued for at least six weeks for women with previous thromboembolic events. Thus, it was reasonable in our case to treat with LMWH at the antepartum and postpartum period.

Our review of the literatures indicated that only two cases with protein S deficiency were complicated with thromboembolic events following ovulation induction (Table 1) [16,17]. Differently to these two cases, our case had the complication of OHSS, but finally gave live births at 34 weeks of gestation.

In conclusion, thromboembolism is one of the critical complications among women with OHSS. Inherited thrombophilia is a rare disease and it is also a risk factor for thromboembolism. We demonstrate this case to emphasize the good outcomes of achieving live births in a case with underlying protein S deficiency and thromboembolism after OHSS. Clinical obstetricians should pay more attention to the possibility of inherited thrombophilia when women with thromboembolism after OHSS.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201800210B0).

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Authors’ contribution

K.C. Lan and K.L. Huang wrote the first draft of the paper. K.L. Huang collected patient's profile and associated data. K.C. Lan, T.Y.

Hsu, C.C. Tsai and Y.C. Ou reviewed literatures and illustrated the table. All authors contributed to the revising of this manuscript and approved the final submission.

Declaration of competing interest

The authors declare that they have no competing interests.

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